The University of Osaka

Immunology Frontier Research Center

Annual Report of IFReC 2024-2025

wpi World Premier International Research Center Initiative

WPI The University of Osaka iFReC

CONTENTS

Message from the Director

As the Director of the Immunology Frontier Research Center (WPI-IFReC) at the University of Osaka, I am very pleased to present the IFReC Annual Report for fiscal year 2024. Since joining the WPI Academy in 2017, we at IFReC have pioneered a unique academic-industry partnership that unleashes new possibilities in collaborative research. It is gratifying that we hosted a site visit by the WPI program in January 2025, and that many of our efforts and research achievements were highly evaluated by the committee members.

IFReC goes beyond basic research and social engagement, and aims to significantly contribute to our university's educational system by developing graduate programs specifically for international students specializing in immunology. This project commenced in 2024, with the first cohort of graduate students scheduled to be admitted from 2025 onwards. We expect this to be a promising project in the future.

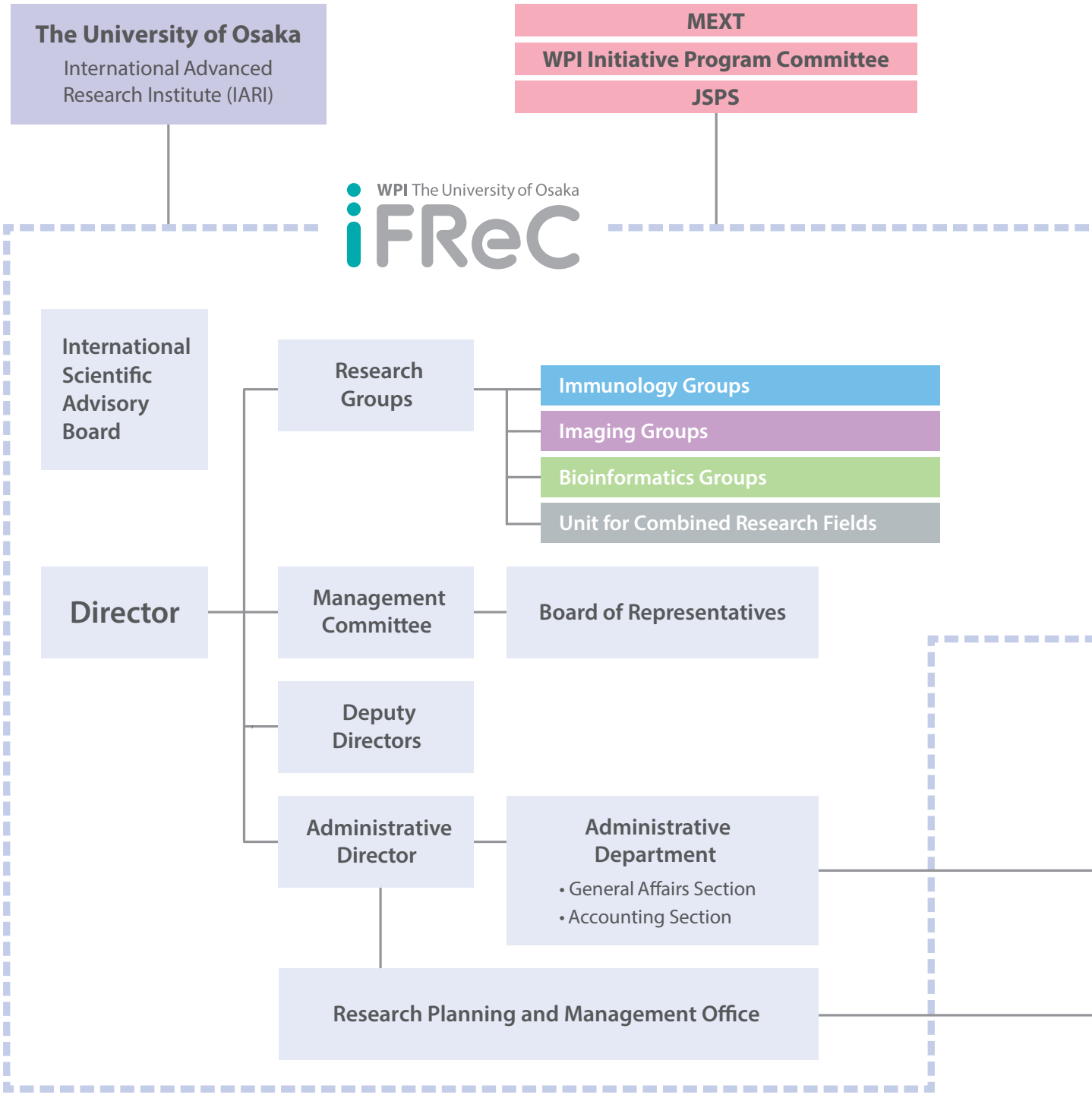
IFReC and ImmunoSensation^2 (University of Bonn) again co-organized "The Third International School on Advanced Immunology" in FY2024. This event will contribute to the development of many young researchers, and will strengthen future ties between the research institutions in Osaka and Bonn. Additionally, IFReC co-organized "The Third University College London - Osaka University Joint Symposium on Immunology" in Osaka. Moreover, we successfully hosted "The International Symposium on Microbiology and Immunology," our 14th international symposium. These events brought together international researchers and facilitated high-level discussions on the frontiers in immunology.

IFReC plays a central role in immunology and infectious disease research, fostering collaborations among various research departments and institutes such as the Research Institute for Microbial Diseases (RIMD), the Center for Infectious Diseases Education and Research (CiDER) and the Center for Advanced Modalities and DDS (CAMaD) at the University of Osaka. We are committed in our efforts to continue basic research in immunology and to seek ways to make meaningful contributions to society, and through research and education, we will drive the advancement of science and shape the future of immunology research worldwide.

Kiyoshi TAKEDA, MD/ PhD
Director
WPI Immunology Frontier Research Center
The University of Osaka

Organization

Organization Chart



Cooperative Institutions

- Institute for Frontier Life and Medical Sciences, Kyoto University, Japan
- RIKEN Center for Integrative Medical Sciences, Japan
- University College London, UK
- ImmunoSensation^2, Cluster of Excellence, the Rheinische Friedrich-Wilhelms-University of Bonn, Germany
- The Peter Doherty Institute for Infection and Immunity, the University of Melbourne, Australia
- Korea Advanced Institute of Science and Technology

As of April 2025

Joint Research Chairs with the Pharmaceutical Companies

- Innovative Drug Discovery in Immunology (Chugai Pharma)
- Immune-Therapeutic Drug Discovery (Otsuka Pharma)
- Innate Immunity
- Innovative Drug Discovery in Host Defense

Common Facilities

- Core Instrumentation Facility
- Animal Resource Center for Infectious Diseases
- Network Administration Office

Administrative Office

General Affairs Section

- Employment and acceptance procedures for researchers and staff
- Social insurance (for part-time staff), employment insurance
- Various research support (MTA, patents, animal experiments, safety etc.)
- Support for international researchers and students
- IFReC Kishimoto Foundation Fellowship Program

Accounting Section

- Budget drafting / implementation / management
- Acceptance and implementation of third-party funding
- Purchasing and payment of payroll, travel expense and honorarium
- Health insurance procedures
- Management of facilities

Research Planning and Management Office

- Research promotion and support (consultation for grants and patents, etc.)
- Establishing research environments (facility and safety management, research agreement, etc.)
- Fostering young scientists (Winter School, Advanced Postdoc Program, orientation, etc.)
- Organizing scientific events (symposia, colloquia, seminars, etc.)
- Public relations (publishing, website, outreach to citizens, etc.)

Committees & Advisory Board for IFReC

The World Premier International Research Center Initiative (WPI)

Program Director

As of November, 2024

Akira UKAWA	WPI Program Director and Academy Director

Program Committee Members

Michinari HAMAGUCHI (Chairperson)	Director General, Strategic Center Biomedical Advanced Vaccine Research and Development for Preparedness and Response(SCARDA), Japan Agency for Medical Research and Development (AMED) Councelor to the President, Japan Science and Technology Agency (JST)
Mariko HASEGAWA	President, Japan Arts Council
Kazuhiko ISHIMURA	President, National Institute of Advanced Industrial Science and Technology
Takaaki KAJITA	Professor, Institute for Cosmic Ray Research, The University of Tokyo Nobel laureate in Physics (2015)
Maki KAWAI	President, National Institutes of Natural Sciences
Motoko KOTANI	Executive Vice President, Tohoku University
Ryozo NAGAI	President, Jichi Medical University
Rita COLWELL	Distinguished University Professor, University of Maryland, USA
Richard DASHER	Director, US-Asia Technology Management Center, Stanford University, USA
Victor Joseph DZAU	President, National Academy of Medicine, USA
Pavel KABAT	Secretary-General, International Human Frontier Sciences Program Organization (HFSPO), France
Matthias KLEINER	University Professor, Technical University Dortmund, Germany
LIM Chuan Poh	Chairman, Singapore Food Agency (SFA)
Mona NEMER	Chief Science Advisor, Government of Canada
Jean ZINN-JUSTIN	Scientific adviser, Institute of Research into the Fundamental Laws of the Universe (IRFU/CEA), France

WPI Academy

In 2017, MEXT established the WPI Academy to be the vanguard in internationalizing and further renovating Japan's research environment. The WPI Academy is a much-anticipated upgrade of WPI institutes, and is expected to position Japan as a hub at the pinnacle of international researcher circulation. In the decade ahead, the research institutes of WPI and WPI Academy will work together to hold public relations and outreach activities.

Program Officer for IFReC

Kouji MATSUSHIMA	Professor, Research Institute for Biomedical Sciences, Tokyo University of Science

International Scientific Advisory Board for IFReC

As of March, 2025

Lewis LANIER	University of California, San Francisco, USA
Anne O'GARRA	The Francis Crick Institute, UK
Jeffrey RAVETCH	Rockefeller University, USA
Art WEISS	University of California, San Francisco/Howard Hughes Medical Institute, USA
Joachim SCHULTZ	DZNE/LIMES Institute, University of Bonn, Germany
Kayo INABA	Japan Agency for Medical Research and Development, Japan
Kazuhiko YAMAMOTO	RIKEN Center for Integrative Medical Sciences, Japan
Osamu OHARA	Kazusa DNA Research Institute, Japan
Hiroshi KIYONO	Future Medicine Education and Research Organization at Chiba University, Japan

In Memory of Dr. Fritz Melchers

Dr. Fritz Melchers, an internationally renowned immunologist who made significant contributions to IFReC since its establishment, has passed away on February 24. We have received a memorial message from Dr. Tadamitsu Kishimoto, a longtime friend of Dr. Melchers.

At the end of February 2025, I was stunned to hear from a friend at the Max Planck Institute in Berlin that Fritz Melchers had passed away. We had been close friends since 1980, and we shared a deep research interest in the field of B lymphocyte immunology.

During the 1980s and 1990s, I often traveled to Europe and always made a point of visiting the Basel Institute for Immunology. Fritz served as the director of that institute for 20 years, from 1980 until its closure in 2000, making significant contributions both to the institute's development and to the advancement of immunology as a whole. Many of my colleagues conducted their research there.

Another colleague and fellow B lymphocyte researcher, Dr. William E. Paul of the U.S. National Institutes of Health, passed away ten years ago. I recall how, at an International Congress of Immunology in the 1980s, Fritz, William, and I discussed proposing the names BSF-1, BSF-2, and so on for the molecules that activate B lymphocytes.

Fritz also supported the Japanese Society for Immunology and provided travel grants through the Melchers Travel Award, enabling young Japanese researchers to study abroad.

Both Fritz and Bill were three years my senior, and I never imagined I would lose them both. While it is natural for life to come to a close in one's late eighties, as someone of the same generation, I feel an indescribable sense of sadness at their passing. Yet their outstanding contributions to immunology, especially in the field of B lymphocyte research, will live on for generations to come. Even after their passing, their scientific achievements will undoubtedly remain in immunology textbooks.

Dr. Tadamitsu Kishimoto and Dr. Fritz Melchers
(at the IFReC International Symposium 2012 (L) and 2016 (R), respectively)

Laboratories

As of March 2025

Host Defense

Shizuo Akira, MD/PhD

Professor	Shizuo Akira
Associate Professor	Kazuhiko Maeda
Assistant Professor	Akihiko Murata
Postdoctoral Fellow	1
Research Assistant	3
Visiting Scientist	4
Support Staff	3

Our research focuses on understanding host defense mechanisms against pathogens through both innate and adaptive immunity and developing therapeutic strategies for immune-related disorders. A central theme of our work is the role of Regnase-1, an RNA-binding protein essential for immune homeostasis. Regnase-1 degrades specific inflammatory mRNAs, thereby modulating immune responses. This year, we investigated its function in natural killer (NK) cells, explored the impact of its RNase activity using a nuclease-null mutant, and examined its self-regulatory mechanisms.

Role of Regnase-1 in NK Cells

We examined the role of Regnase-1 in NK cell-mediated anti-tumor immunity using mice with NK cell-specific deletion of *Regnase-1* (*Reg1*$^{\Delta NK}$). These mice exhibited enhanced NK cell function, with increased production of IFN-γ and cytolytic proteins. Both splenic and tumor-infiltrating NK cells in *Reg1*$^{\Delta NK}$ mice showed an activated phenotype and upregulated cytotoxic gene expression. A notable finding was the increased expression of the chemokine receptor CXCR6 in *Reg1*$^{\Delta NK}$ NK cells, which promoted their infiltration into tumor tissues. This infiltration was dependent on IFN-γ signaling; blocking IFN-γ impaired NK cell accumulation and CXCL16 expression in the tumor microenvironment. Furthermore, the transcription factors OCT2 and IκBζ were upregulated in *Regnase-1*-deficient NK cells and were found to form a complex with NF-κB, enhancing *Ifng* transcription. These results establish Regnase-1 as a negative regulator of NK cell effector functions and tumor infiltration. Inhibiting Regnase-1 could provide a novel approach to enhancing NK cell-based therapies, such as the development of *Regnase-1*-deficient CAR-NK cells for the treatment of solid tumors.

Role of Nuclease-Null Regnase-1

To investigate the significance of Regnase-1's RNase activity, we created mice with a D141N point mutation in its catalytic domain, which abolishes its endonuclease function. These mutant mice developed systemic inflammation characterized by immune cell infiltration and granuloma formation, particularly in the lungs. $CD4^+$ T cells from these mice displayed mTORC1 pathway hyperactivation and autoimmune-like features. RNA-seq analysis identified *Pim2*, a serine/threonine kinase, as highly upregulated in $CD4^+$ T cells. Inhibiting Pim2 activity reduced granulomatous inflammation, immune cell infiltration, and adhesion molecule expression on $CD4^+$ T cells in the lungs. Our data confirmed *Pim2* as a direct target of Regnase-1, linking its dysregulation to increased immune cell adhesion and migration. These findings underscore the critical role of Regnase-1's RNase activity in preventing immune dysregulation and suggest that targeting Pim2 may offer a therapeutic strategy for inflammatory diseases caused by impaired RNA degradation.

Autoregulation via the 3'UTR of *Regnase-1*

We also investigated how Regnase-1 regulates its own expression. By generating mice with a two-base pair deletion in the stem-loop (SL) region of the *Regnase-1* 3'UTR—required for self-cleavage—we disrupted its autoregulation. This mutation increased the stability of *Regnase-1* mRNA, leading to higher mRNA and protein levels in mouse embryonic fibroblasts (MEFs). Despite increased Regnase-1 levels, hematopoietic differentiation remained unaffected. Additionally, expression of *Il6*, a target of Regnase-1, was suppressed in the mutant MEFs, suggesting a reinforced negative feedback loop. These mutant mice provide a

valuable in vivo model for studying the consequences of Regnase-1 overexpression, and further analyses are underway using models of skin and lung inflammation.

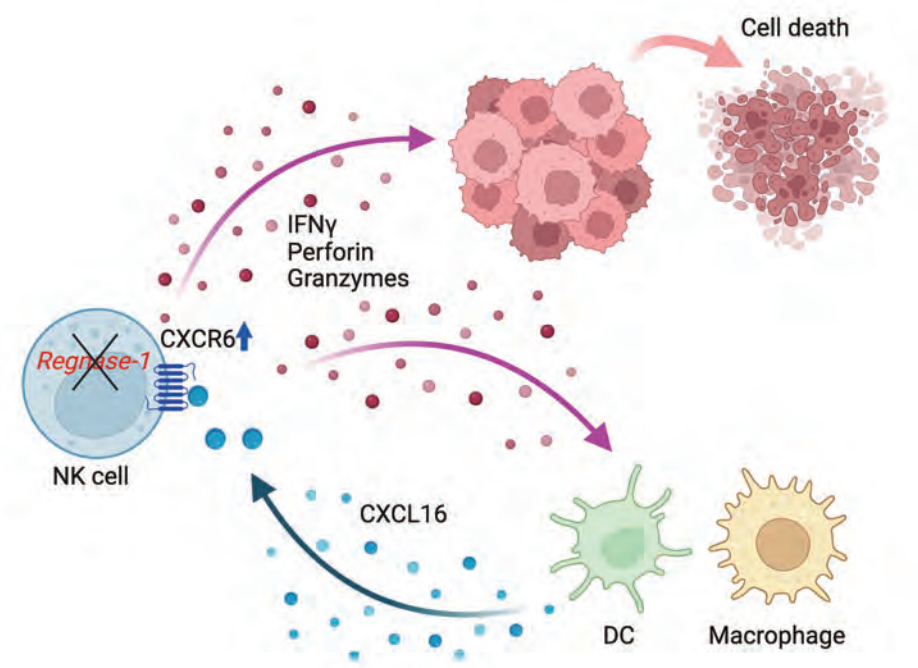


Figure.
The accumulation of NK cells and their heightened production of cytotoxic proteins within the tumor microenvironment bolster the anti-tumor activity of Reg1$^{\Delta NK}$.

Recent Publications

1. Sakaguchi T, et al. Novel choline- deficient and 0.1%-methionine-added high-fat diet induces burned-out metabolic-dysfunction-associated steatohepatitis with inflammation by rapid immune cell infiltration on male mice. Nutrients 16:4151 (2024).
2. Sun X, et al. Deletion of the mRNA endonuclease Regnase-1 promotes NK cell anti-tumor activity via OCT2-dependent transcription of Ifng. Immunity 57:1360-1377 (2024).
3. Lu Y, et al. CGRP sensory neurons promote tissue healing via neutrophils and macrophages. Nature 628:604-611 (2024).
4. Kawai T, et al. Decoding Toll-like receptors: Recent insights and perspectives in innate immunity. Immunity 57:649-673 (2024).
5. Akira S and Maeda K. Control of RNA stability in immunity. Ann Rev Immunol. 39:481-509 (2021).

Immunopathology

Atsushi Kumanogoh, MD/PhD

Professor	Atsushi Kumanogoh
Assistant Professor	Kohei Tsujimoto
Research Assistant	5
Support Staff	5

Our research team is involved in two approaches, basic and clinical immunology. As a fundamental aspect of our projects, we propose to study the regulation of immune cell motility and migration in vivo by soluble and membrane-bound 'immune guidance molecules' such as semaphorins and their receptors. Semaphorins were originally identified as axon guidance molecules that function during neuronal development. However, accumulating evidence suggests that semaphorins are also involved in immune responses, both physiological and pathological, and they are now considered potential diagnostic and/or therapeutic targets for a number of diseases. Beyond such fundamental implications, we are trying to apply the findings from this proposed study to the diagnosis/therapy of human immunological disorders, such as autoimmunity, allergy, immunodeficiency, cancer/metastasis, and neurodegenerative diseases. In a study in ***Neutron*** 2024, we found that SEMA6D is a pleiotropic gene for psychiatric and metabolic traits in human. Loss of SEMA6D elevates anxiety, mitigates obesity, and enhances myelopoiesis in mice. Amygdalar SEMA6D regulates anxiogenic and autonomic responses and SEMA6D controls synaptic maturation and GABAergic transmission in the amygdala. These results demonstrate that SEMA6D is important for the normal functioning of the neural circuits in the amygdala, coupling emotional, metabolic, and inflammatory responses.

In addition, we have recently been focusing on how to translate the findings from the bench to the bedside. In this research context, we have performed single-cell analysis in patients with ANCA-associated vasculitis. In a study in ***Nature Communications*** 2025, we investigated which cell types dominate the blood of patients in the early stages of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which is caused by inflammation in the blood vessels and can affect organ function. We recruited six patients and seven healthy controls. We collected about 180,000 white blood cells and performed single-cell analyses to characterize them genetically and to look at the proteins on the cell surface. These transcriptome and proteome analyses revealed significantly higher proportions of two specific neutrophil subpopulations in the patients compared to the healthy individuals. We discovered an increase in a highly activatable subset of neutrophils can be stimulated by interferon-gamma (Figure). Three of the patients with the highest expression of interferon-gamma response genes had persistent vasculitis symptoms after treatment, indicating that this neutrophil subpopulation is involved in persistent vasculitis. Interferon-gamma levels were measured in stored serum samples from 37 patients. Of the 24 new-onset patients studied, the top six patients with the highest serum interferon-gamma concentrations all experienced relapses, suggesting that measuring the concentration of interferon-gamma in the blood could help us predict disease relapse. Our research is advancing our understanding of the immune mechanisms driving ANCA-associated vasculitis. By identifying specific neutrophil populations and their role in disease progression, these findings may lead to more personalized treatment strategies and better patient outcomes.

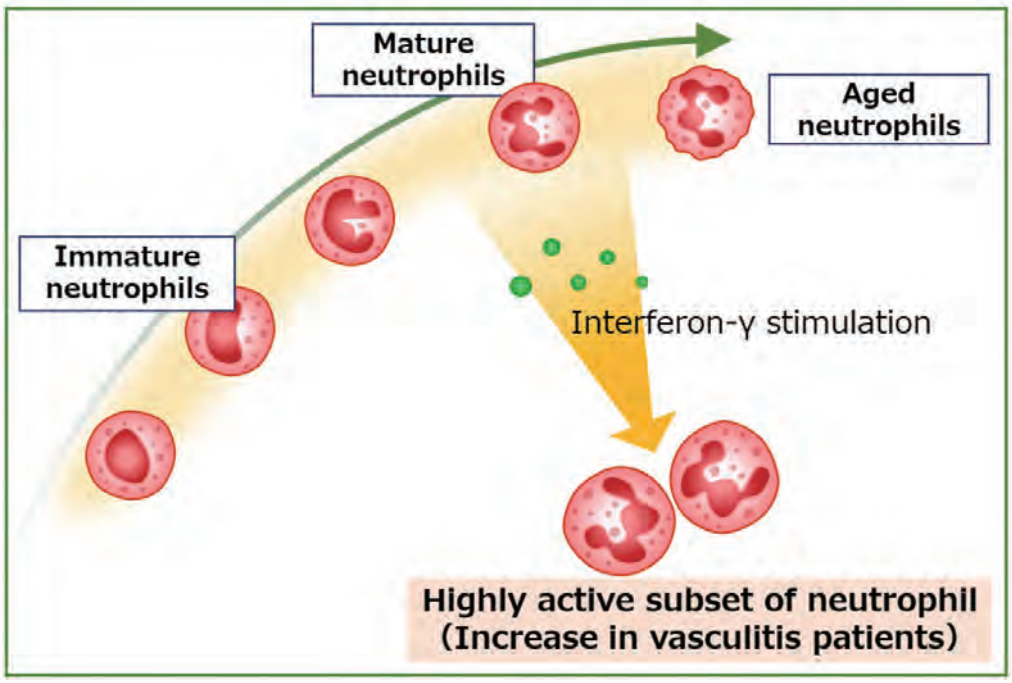


Figure.
Single-cell analysis of neutrophils identifies an increased population of interferon-gamma related subset in patients with newly diagnosed vasculitis.

Recent Publications

1. Nishide M, Nishimura K, Matsushita H, Kawada S, Shimagami H, Metsugi S, Kato Y, Kawasaki T, Tsujimoto K, Edahiro R, Shirai Y, Itotagawa E, Naito M, Yamamoto Y, Matsukawa K, Omiya R, Okada Y, Hattori K, Narazaki M, Kumanogoh A. Neutrophil single-cell analysis identifies a type II interferon-related subset for predicting relapse of autoimmune small vessel vasculitis. Nat Commun. 16:3581 (2025).

2. Nishide M, Shimagammi H and Kumanogoh A. Single-cell analysis in rheumatic and allergic diseases: Beyond the sea of data, challenges for clinical application Nature Rev Immunol. 24(11):781-797 (2024).

3. Nakanishi Y, Izumi M, Matsushita H, Koyama Y, Diez D, Takamatsu H, Koyama S, Nishide M, Naito M, Mizuno Y, Yamaguchi Y, Mae T, Noda Y, Nakaya K, Nojima S, Sugihara F, Okuzaki D, Ikawa M, Shimada S, Kang S, Kumanogoh A. Semaphorin 6D tunes amygdalar circuits for emotional, metabolic, and inflammatory outputs. Neuron 112(17):2955-2972.e9 (2024).

4. Naito Y, Koyama S, Masuhiro K, et al. Tumor-derived semaphorin 4A improves PD-1-blocking antibody efficacy by enhancing CD8(+) T cell cytotoxicity and proliferation. Science Adv. 9:eade0718 (2023).

5. Nishide M, Nishimura K, Matsushita H, et al. Single-cell multi-omics analysis identifies two distinct phenotypes of newly-onset microscopic polyangiitis. Nature Commun. 14:5789. 2023.

Immunochemistry

Hisashi Arase, MD/PhD

Professor	Hisashi Arase
Associate Professor	Hui Jin
Assistant Professor	Shunsuke Mori
Postdoctoral Fellow	2
Research Assistant	4
Visiting Scientist	1
Support Staff	4

A) Self and Neoself Discrimination by T Cells in the Pathogenicity of Autoimmune Diseases

MHC class II allelic polymorphisms have been associated with susceptibility to many autoimmune diseases. We have found that misfolded cellular self-antigens can be presented on MHC class II molecules in the absence of the invariant chain. Moreover, these misfolded proteins, when displayed on MHC class II molecules, serve as targets for autoantibodies in several autoimmune diseases, including rheumatoid arthritis, antiphospholipid syndrome, ANCA-associated vasculitis, and Graves' disease (*PNAS* 2014; *Blood* 2015; *Arthritis Rheumatol* 2017; *Arthritis Rheumatol* 2021; *Science Advances* 2022). We have termed these aberrantly presented proteins "neoself" antigens. More importantly, our findings indicate that T cells are capable of discriminating between normal self-peptide antigens and neoself antigens presented on MHC class II molecules, and that T cell responses against neoself antigens drive autoimmunity. In fact, approximately 10% of clonally expanded T cells in lupus patients recognize neoself antigens, suggesting that these are primary targets for autoreactive T cells (Figure 1, *Cell* 2024). These observations provide a paradigm shift in our understanding of T cell recognition of self-antigens.

B) Studies on Host-Pathogen Interactions

The immune system has coevolved with infectious agents, underscoring the importance of host-pathogen interactions in understanding immune function. We have found that viruses often exploit immune inhibitory receptors not only for evading the immune response but also to facilitate infection (*Cell* 2008; *PNAS* 2010). Moreover, our research indicates that malaria parasites also utilize various inhibitory receptors as part of their immune evasion strategies (*Nature* 2017; *Nature* 2020; *Nature* 2025). Notably, we have observed that human natural killer (NK) cell receptors have coevolved with malaria parasites. Additionally, we have identified a novel immune evasion strategy employed by both bacteria and SARS-CoV-2 that targets antibodies (*Nature Microbiology* 2016; *Cell* 2021, Figure 2). These findings underscore the crucial role of host-pathogen interactions in controlling infectious diseases.

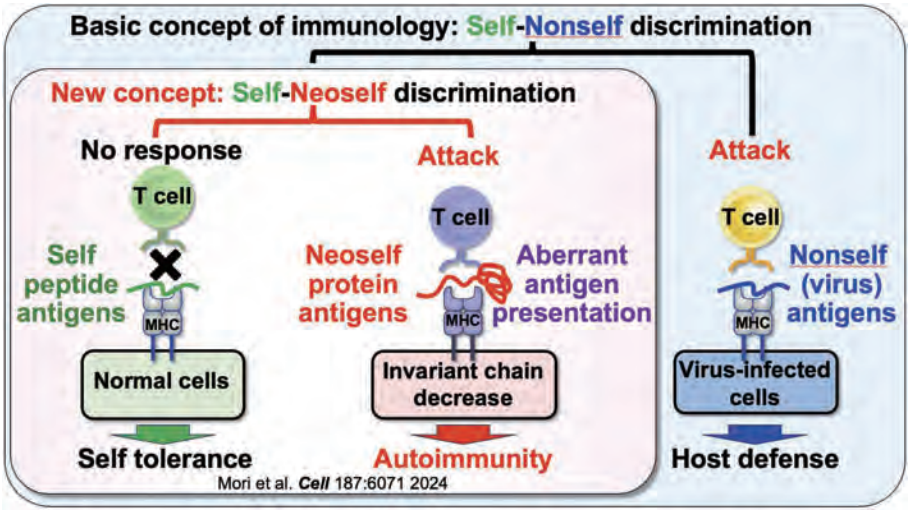


Figure 1.
Self and Neoself Discrimination by T Cells in the Pathogenicity of Autoimmune Diseases.
Self-antigens can be subdivided into self-peptide antigens—normally presented on MHC class II molecules—and neoself antigens, which are aberrantly presented on these molecules. T cells are capable of distinguishing between self-peptide and neoself antigens, and their responses against neoself antigens drive autoimmunity (*Cell* 2024).

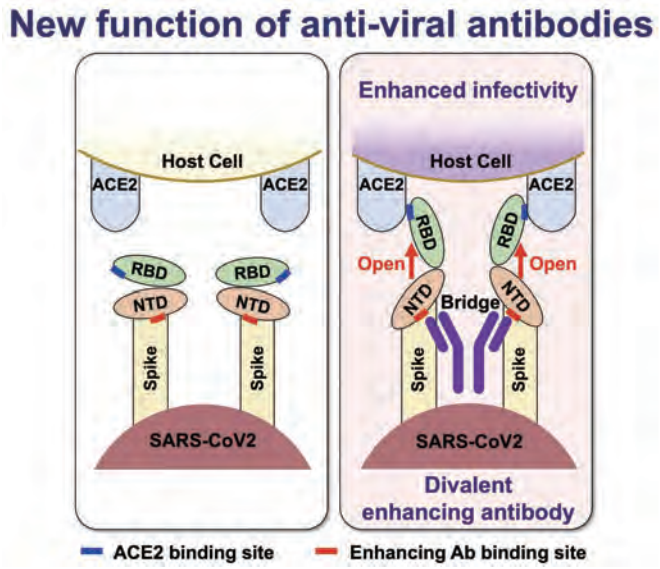


Figure 2.
SARS-CoV-2 infectivity enhancing antibodies.
Certain antibodies targeting the N-terminal domain (NTD) of the spike protein induce a conformational change that promotes the open state of the receptor-binding domain (RBD), thereby enhancing the infectivity of SARS-CoV-2 (*Cell* 2021).

Recent Publications

1. Mori S, Kohyama M, Yasumizu Y, Tada A, Tanzawa K, Shishido T, Kishida K, Jin H, Nishide M, Kawada S, Motooka D, Okuzaki D, Naito R, Nakai W, Kanda T, Murata T, Terao C, Ohmura K, Arase N, Kurosaki T, Fujimoto M, Suenaga T, Kumanogo A, Sakaguchi S, Ogawa Y, Arase H: Neoself-antigens are the primary target for autoreactive T cells in human lupus. Cell 187:6071-6087 (2024).

2. Jin H, Kishida K, Arase N, Matsuoka S, Nakai W, Kohyama M, Suenaga T, Yamamoto K, Sasazuki T, Arase H. Abrogation of self-tolerance by misfolded self-antigens complexed with MHC class II molecules. Sci Adv. 8(9):eabj9867 (2022).

3. Liu Y, Soh WT, Tada A, Arakawa A, Matsuoka S, Nakayama EE, Li S, Ono C, Torii S, Kishida K, Jin H, Nakai W, Arase N, Nakagawa A, Shindo Y, Kohyama M, Nakagami H, Tomii K, Ohmura K, Ohshima S, Okada M, MatsuuraY, Standley DM, Shioda T, Arase H. An infectivity-enhancing site on the SARS-CoV-2 spike protein is targeted by COVID-19 patient antibodies. Cell 184:3452-3466 (2021).

4. Saito F, Hirayasu K, Satoh T, et al. Immune evasion of Plasmodium falciparum by RIFIN via inhibitory receptors. Nature 552:101-105 (2017).

5. Hirayasu K, Saito F, Suenaga T, et al. LILRA2 is an innate immune sensor for microbially cleaved immunoglobulins. Nat Microbiol. 1:1-7 (2016).

Immune Regulation

Tadamitsu Kishimoto, MD/PhD
Sujin Kang, PhD

Professor	Tadamitsu Kishimoto
Associate Professor	Sujin Kang
Assistant Professor	Hozaifa Metwally
Research Assistant	1
Visiting Scientist	1
Support Staff	3

1. Dysfunction of brain vascular and choroid plexus cells in sepsis-associated encephalopathy

Understanding the mechanism behind sepsis-associated encephalopathy (SAE) remains elusive. This study sheds light on the complex cellular and molecular alterations that occur in the brains of a mouse model with SAE, ultimately unraveling the underlying mechanisms of cognitive defects in this condition. We established a murine model using cecal ligation puncture (CLP) in wild-type mice and collected brain tissues for analysis at 2 days, and 7 days post-surgery. Utilizing advanced techniques such as single-cell RNA sequencing (scRNA-seq) and bulk RNA-seq, we conducted a comprehensive characterization of the cellular responses and molecular patterns within the brain. Our study uncovered notable links between vein endothelial cells (ECs) and choroid plexus cells during SAE. We observed a significant increase in lipocalin-2 (Lcn2) expression in brain vein ECs by IL-6 receptor trans-signaling. In addition, brain vein ECs of SAE mice exhibited the accumulation of lipid droplets and their inhibition suppressed the LCN2 production. Moreover, through further analysis, we discovered significant upregulation of ligand-receptors between Lcn2-Slc22A17 which is highly expressed in choroid plexus cells. On day 2 after CLP, choroid plexus cells increased the expression of the K+ channel and activated ion metabolic pathway, compared to control mice. Additionally, we noted elevated serum levels of IL-6 and LCN2 in SAE patients, compared to those of sepsis patients. Our findings suggest the potential association between vein ECs and choroid plexus cells as an important pathway driving cognitive defects of SAE and highlight the potential of targeting the LCN2-SLC22A17 axis for therapeutic intervention (Figure).

2. The role of gp130 signaling in pericytes during the pulmonary fibrosis

During the formation of pulmonary fibrosis (PF), disturbed vascular integrity and altered micro-vessels contribute to endothelium injury, vascular leakage, and dysregulated tissue fibrosis. Pericytes are the vascular mural cells that are embedded in the basement membrane outside the blood micro-vessel. Although pericytes are well-known to promote angiogenesis and maintain vascular homeostasis, their role in PF is largely unknown. Here, we identified the protective role of gp130 signaling in pericytes, which effectively inhibit PF through regulating immune cell function. By establishing bleomycin-induced lung fibrosis model, we found that pericyte-specific gp130 deletion in mice (*gp130*^{pKO} mice) showed higher mortality, severe body weight loss, increased vascular permeability and accelerated collagen depositions compared with control mice. Using scRNA-seq analysis, we identified the altered population in non-immune cells and immune cells between bleomycin-treated *gp130*^{pKO} mice and control mice. Notably, we found that *gp130*^{pKO} mice showed an increased population of neutrophils. Using time course study, we verified the emergence of neutrophils were positively correlated with fibrosis progression and found that neutrophils were hyper-activated in the context of pro-inflammatory cytokine expression in *gp130*^{pKO} mice. At the late stage of PF, we identified the increased population of interstitial macrophages in *gp130*^{pKO} mice that showed significant fibrotic phenotype compared with control mice. Together, our findings advance the crucial role of gp130 signaling in pericytes, protecting against PF via inhibition of neutrophils and interstitial macrophages activation.

3. Threonine Phosphorylation of STAT1 Restricts Interferon Signaling and Promotes Cell-specific Inflammatory Responses

Signal transducer and activator of transcription (STAT) proteins are versatile signaling molecules that regulate cellular decisions across eukaryotes, exhibiting remarkable modularity and plasticity. Traditionally, their function has been framed within a binary extracellular signaling model, centered on JAK-mediated tyrosine phosphorylation versus the "unphosphorylated" state. This perspective has constrained our understanding of their broader roles and therapeutic potential. Recently, we identified Thr748 (Thr749 in humans) phosphorylation as a JAK-independent switch within STAT1—a key regulatory mechanism that orchestrates distinct immune and non-immune cellular responses during infection, inflammation, and autoimmunity. Using genetically engineered mice expressing a phospho-deficient threonine748-to-alanine (T748A) Stat1 mutant, as well as STAT1-deficient mice, combined with extensive biochemical analyses, our research demonstrates a phosphorylation-dependent modularity that shapes STAT1's context-dependent and cell-specific functions. In sepsis, STAT1 threonine phosphorylation restricts its canonical JAK-mediated tyrosine phosphorylation and promotes the expression of inflammatory mediators at the expense of anti-inflammatory ones in macrophages following LPS stimulation. In intestinal inflammation, STAT1 threonine phosphorylation limits JAK-mediated tyrosine phosphorylation while promoting the expression of structural integrity genes in gut epithelial cells following chemically induced damage. In pristane-induced lupus, a disease largely driven by JAK-mediated STAT1 activation, threonine phosphorylation appears dispensable for STAT1 functionality. Collectively, our findings suggest a phosphorylation-dependent modularity that governs the spectrum of STAT1 function in inflammatory contexts: an IFN-driven, phospho-tyrosine-dependent signaling and an inflammatory, phospho-threonine-dependent signaling, with the threonine phosphorylation selectively driving inflammatory activities.

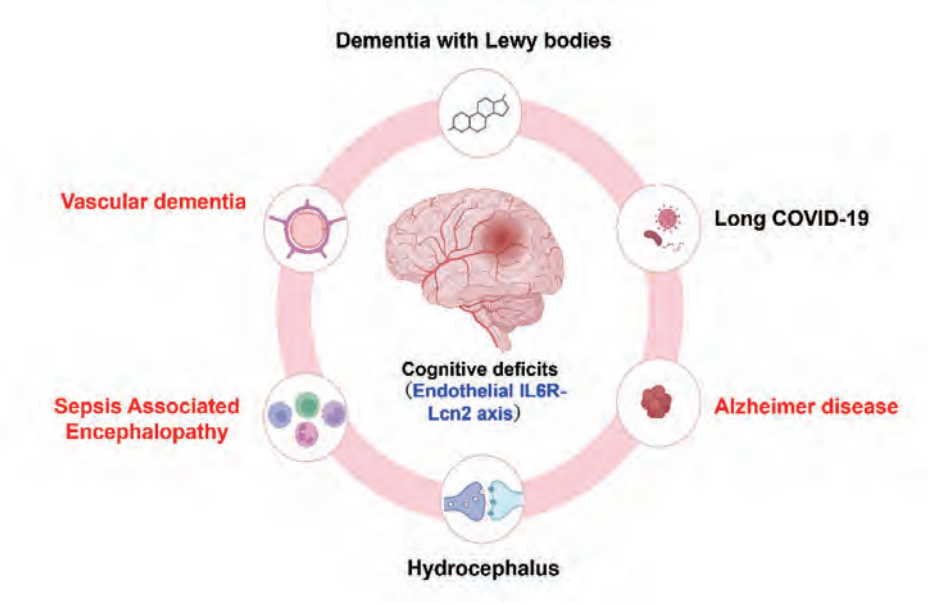


Figure.
Brain endothelial cell inflammatory responses contribute to the pathology of cognitive deficits.

Recent Publications

1. Kang S, Onishi S, Ling Z, Inoue H, Zhang Y, Chang H, Zhao H, Wang T, Okuzaki D, Matsuura H, Takamatsu H, Oda J, Kishimoto T. Gp130-HIF1α axis-induced vascular damage is prevented by the short-term inhibition of IL-6 receptor signaling. Proc Natl Acad Sci USA. 121(2):e2315898120 (2024).

2. Metwally H, Elbrashy, MM, Ozawa T, Okuyama K, White JT, Tulyeu J, Søndergaard JN, Wing JB, Muratsu A, Matsumoto H, Ikawa M, Kishi H, Taniuchi I and Kishimoto T. Threonine Phosphorylation of STAT1 Restricts Interferon Signaling and Promotes Innate Inflammatory Responses. Proc Natl Acad Sci USA. 121 (17):e2402226121 (2024).

3. Ishibashi T, Inagaki T, Okazawa M, Yamagishi A, Ohta-Ogo K, Asano R, Masaki T, Kotani Y, Ding X, Chikaishi-Kirino T, Maedera N, Shirai M, Hatakeyama K, Kubota Y, Kishimoto T*, Nakaoka Y*. IL-6/gp130 signaling in CD4+ T cells drives the pathogenesis of pulmonary hypertension. Proc Natl Acad Sci USA. 121(16):e2315123121 (2024). (*equally corresponding author)

Mucosal Immunology

Kiyoshi Takeda, MD/PhD

Professor	Kiyoshi Takeda
Associate Professor	Hisako Kayama
Assistant Professor	Ryu Okumura
	Mari Murakami
	Taiki Sakaguchi
Postdoctoral Fellow	4
Research Assistant	6
Visiting Scientist	1
Support Staff	2

The intestinal lumen is rich in gut microbial metabolites that serve as signaling molecules for gut immune cells. G-protein-coupled receptors (GPCRs) sense metabolites and can act as key mediators that translate gut luminal signals into host immune responses. However, the impacts of gut microbe–GPCR interactions on human physiology have not been fully elucidated. Using human induced pluripotent stem cell (iPSC)-derived cDC1s and a monolayer human gut organoid coculture system, we show that intestinal type 1 conventional dendritic cells (cDC1s) extend their dendrites toward pyruvate (PA) on the luminal side, forming transepithelial dendrites (TED). Accordingly, GPR31 activation via PA enhances the fundamental function of cDC1 by allowing efficient uptake of gut luminal antigens through TED formation. Our results highlight the role of GPCRs in tuning the human gut immune system according to local metabolic cues.

GPR31 is specifically expressed on cDC1s in human intestinal mononuclear phagocytes

To systematically evaluate human intestinal mononuclear phagocytes, we performed scRNA-seq analysis on cells isolated from the human ileum. Although most GPCR-encoding genes were ubiquitously expressed on cells in various clusters, *GPR31* was specifically expressed in cDC1s. Analysis using a publicly accessible multitissue scRNA-seq dataset of human immune cells showed that *GPR31* was highly expressed in cDC1s, especially in the intestinal lamina propria. These results led us to assume that GPR31 specifically influences human intestinal cDC1 activity in response to gut luminal metabolites. Further analysis confirmed that *GPR31*$^{+}$ cDC1s exhibited enhanced antigen processing and presentation pathways, suggesting that *GPR31* expression on cDC1s could enhance their antigen processing and presentation capacities.

Pyruvate stimulation caused GPR31-dependent dendrite protrusion in human cDC1s

Since GPR31 is activated by bacterial metabolites such as PA and lactate, we examined whether PA influences cDC1 function. Bulk RNA-seq analysis of human cDC1s after PA stimulation revealed upregulation of genes related to dendrite formation, suggesting increased phagocytic ability. Furthermore, PA stimulation significantly enhanced dendrite elongation in cDC1s. To investigate whether the PA–GPR31 axis mediates dendrite protrusion in cDC1s, cDC1s with drug-inducible GPR31 were generated using human iPSCs. Morphological analysis of GPR31-expressing iPSC-derived cDC1s under PA stimulation showed a significant increase in dendrite protrusion, confirming GPR31-mediated regulation. In contrast, LPS stimulation, which generally activates DCs, did not induce dendrite protrusion. These findings demonstrate that PA promotes dendrite protrusion in human intestinal cDC1s through GPR31 activation, highlighting a specific signaling mechanism distinct from general DC activation pathways.

cDC1s internalized antigens via the PA–GPR31 axis

Immunohistochemical analysis revealed that some cDC1s extended dendrites between epithelial layers, suggesting their potential role in recognizing luminal substances. To confirm whether cDC1s extend dendrites toward PA, a co-culture model of cDC1s and the intestinal epithelium derived from human small intestinal organoids was established using cell culture inserts. This co-culture model demonstrated that cDC1s form TEDs in a PA- and GPR31-dependent manner, indicating that the PA–

GPR31 axis mediates TED formation in human intestinal cDC1s. Furthermore, despite the presence of an epithelial barrier, GPR31-expressing cDC1s displayed antigen uptake. These results indicated that the recognition and uptake of intraluminal antigens by human intestinal cDC1s were enhanced by increased TED protrusion via the PA–GPR31 axis. Since cDC1s play a crucial role in cross-priming $CD8^+$ T cells, the potential influence of the PA–GPR31 axis on $CD8^+$ T cell activation was investigated. Immunohistochemical analysis revealed that cDC1s in the human ileum were in close contact with $CD8^+$ T cells. Furthermore, cDC1s exposed to PA-enhanced antigen uptake activated $CD8^+$ T cells more effectively than those without PA stimulation. These findings suggest that human cDC1s extend dendrites into the lumen to capture antigens, thereby facilitating $CD8^+$ T cell activation via the PA–GPR31 axis.

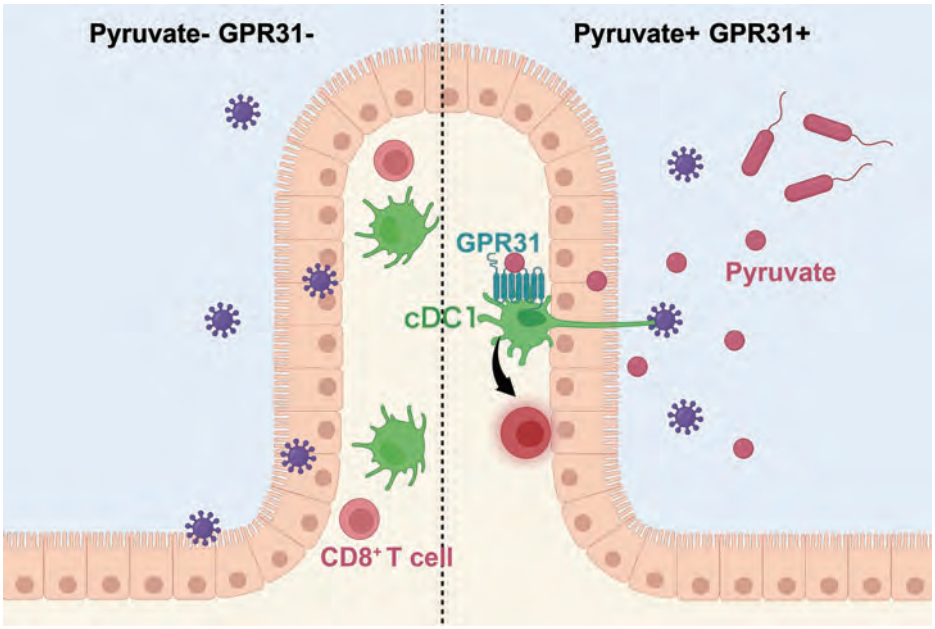


Figure.
Pyruvate-mediated GPR31 activation enhances human intestinal conventional type 1 dendritic cell (cDC1) function by facilitating transepithelial dendrite formation, which improves the uptake of gut luminal antigens.

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1. Oguro-Igashira E, Murakami M, Mori R, Kuwahara R, Kihara T, Kohara M, Fujiwara M, Motooka D, Okuzaki D, Arase M, Toyota H, Peng S, Ogino T, Kitabatake Y, Morii E, Hirota S, Ikeuchi H, Umemoto E, Kumanogoh A, Takeda K. The pyruvate-GPR31 axis promotes transepithelial dendrite formation in human intestinal dendritic cells. Proc Natl Acad Sci USA. 121: e2318767121 (2024).

2. Yokoi T, Murakami M, Kihara T, Seno S, Arase M, Wing JB, Søndergaard JN, Kuwahara R, Minagawa T, Oguro-Igashira E, Motooka D, Okuzaki D, Mori R, Ikeda A, Sekido Y, Amano T, Iijima H, Ozono K, Mizushima T, Hirota S, Ikeuchi H, Takeda K. Identification of a unique subset of tissue resident memory $CD4^+$ T cells in Crohn's disease. Proc. Natl. Acad. Sci. USA 120: e2204269120 (2023).

3. Otake-Kasamoto Y, Kayama H, Kishikawa T, Shinzaki S, Tashiro T, Amano T, Tani M, Yoshihara T, Li B, Tani H, Liu L, Hayashi A, Okuzaki D, Motooka D, Nakamura S, Okada Y, Iijima H, Takeda K*, Takehara T.: Lysophosphatidylserines derived from microbiota in Crohn's disease elicit pathological Th1 response. J Exp Med. 219: e20211291 (2022).

4. Tani H, Li B, Kusu T, Okumura R, Nishimura J, Okuzaki D, Motooka D, Arakawa S, Yoshihara T, Ogino T, Tsai SH, Furuta Y, Muneta M, Nakamura S, Fukusaki E, Yamamoto K, Yagita H, Kayama H and Takeda K. The ATP-hydrolyzing ectoenzyme E-NTPD8 attenuates colitis through modulation of P2X4 receptor-dependent metabolism in myeloid cells. Proc Natl Acad Sci. USA 118: e2100594118 (2021).

5. Morita N, Umemoto E, Fujita S, Hayashi A, Kikuta J, Kimura I, Haneda T, Imai T, Inoue A, Mimuro H, Maeda Y, Kayama H, Okumura R, Aoki J, Okada N, Kida T, Ishii M, Nabeshima R, Takeda K. GPR31-dependent dendrite protrusion of intestinal CX_3CR1^+ cells by bacterial metabolites. Nature 566:110-114 (2019).

Experimental Immunology

Shimon Sakaguchi, MD/PhD

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Postdoctoral Fellow	5
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Visiting Scientist	12
Support Staff	3

Regulatory T (Treg) cells are a functionally distinct $CD4^+$ T-cell subset that plays crucial roles in maintaining immunological self-tolerance and homeostasis by suppressing aberrant or excessive immune responses. The transcription factor (TF) forkhead box protein P3 (Foxp3) is essential for Treg cell function and its loss-of-function mutations cause various immunological diseases such as autoimmunity, allergy and immunopathology in mice and humans primarily due to Treg cell deficiency or dysfunction. Foxp3 forms a large protein complex by interacting with many cofactors, including other TFs and epigenetic regulators. Upon T cell receptor (TCR) stimulation, target genes of the Foxp3 complex are either repressed (e.g., *Il2* and *Ifng*) *or activated* (e.g., *Il2ra* and *Ctla4*). However, it is still unclear how Foxp3 complex acts directly on its target genes to activate or repress in various Treg cell states from development to maturation, and how the interactions of Foxp3 with other TFs, co-activators, and co-repressors control Treg cell function.

The Ikaros TF family has five distinct members: Ikaros (encoded by *Ikzf1*), Helios (*Ikzf2*), Aiolos (*Ikzf3*), Eos (*Ikzf4*), and Pegasus (*Ikzf5*). All are characterized by two sets of highly conserved C2H2 zinc-finger motifs and are crucial for hematopoiesis and adaptive immunity. Ikzf family members, except Ikzf5, are highly expressed in Treg cells and are physically associated with Foxp3. In particular, Helios and Eos contribute to the stability and suppressive function of Treg cells, respectively. Interestingly, a recent attempt through comprehensive mutagenesis showed that variations in the Ikzf1-binding motifs impaired Treg-specific chromatin accessibility. There is also evidence that germline heterozygous mutations in *IKZF1*, especially in the exon 5 region of *IKZF1* (called IkE5), cause immunodeficiency and autoimmune diseases in humans. These findings in mice and humans have prompted us to determine how Ikzf1 and Ikzf3 contribute to Treg cell function and how anomalies in their interactions with Foxp3 may be underlying causes of autoimmune diseases.

We have shown this year that the transcription factor Ikzf1 associates with Foxp3 via its exon 5 (IkE5) and that *IkE5*-deficient Treg cells highly expressed the genes, including *Ifng*, which would otherwise be repressed by Foxp3 upon TCR stimulation. Treg-specific *IkE5*-deletion indeed incurred IFN-γ overproduction, which destabilized Foxp3 expression and impaired Treg suppressive function, causing systemic autoimmune disease. It also evoked strong anti-tumor immunity. In addition, Pomalidomide, which degrades IKZF1 and IKZF3, induced IFN-γ overproduction in human Treg cells. Mechanistically, the Foxp3-Ikzf1-Ikzf3 complex exerted gene-repression by competing with epigenetic co-activators, such as p300, for binding to target gene loci via chromatin remodeling. Collectively, the association of Ikzf1 with Foxp3 is essential for the gene-repressive aspect of Foxp3 function and that the interaction can be a potential target to pharmaceutically control physiological and pathological immune responses, especially in cancer and autoimmune disease settings.

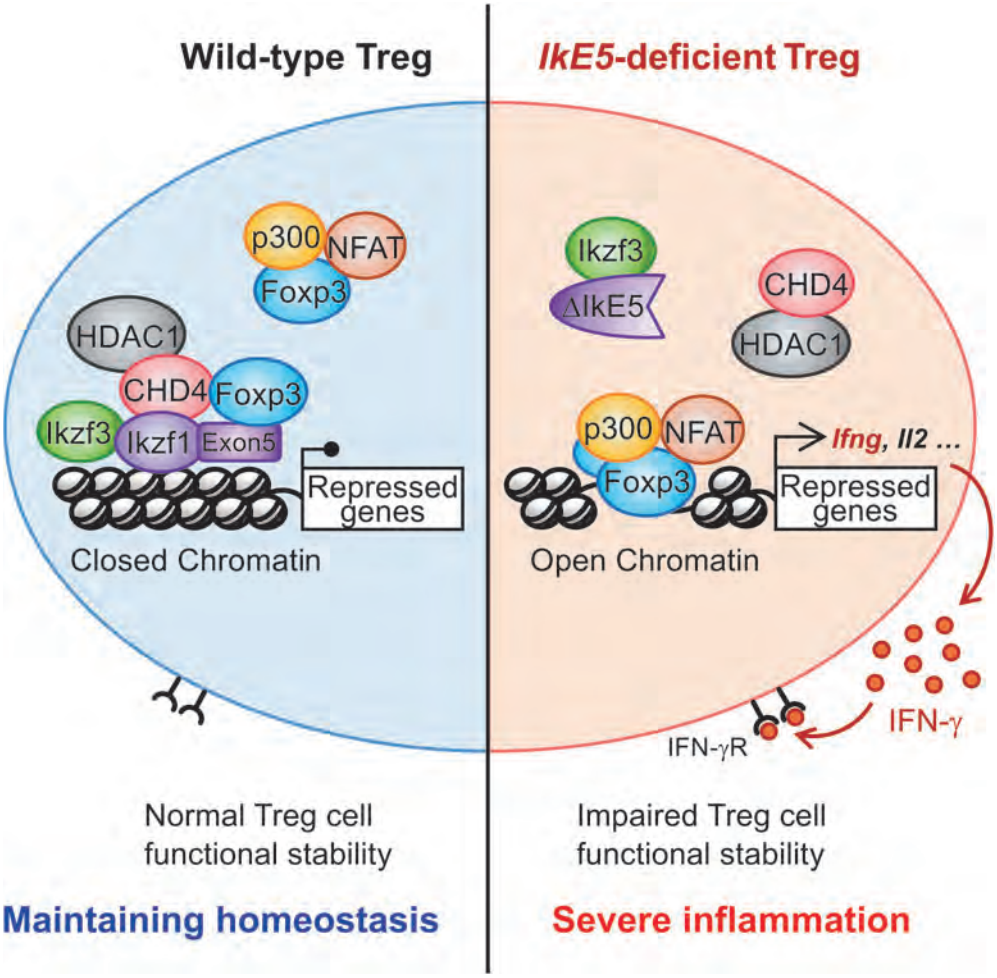

Figure.
Foxp3 associates with the transcription factor Ikzf1 to form a repressive complex. Disruption of the association impairs the functional stability of Treg cells and causes fatal autoimmune disease (Ichiyama et al., *Immunity* 2024).

Recent Publications

1. Chen KY, Kibayashi T, Giguelay A, Hata M, Nakajima S, Mikami N, Takeshima Y, Ichiyama K, Omiya R, Ludwig LS, Hattori K, Sakaguchi S. Genome-wide CRISPR screen in human T cells reveals regulators of FOXP3. Nature (2025) doi: 10.1038/s41586-025-08795-5.

2. Osaki M, Sakaguchi S. Soluble CTLA-4 regulates immune homeostasis and promotes resolution of inflammation by suppressing type 1 but allowing type 2 immunity. Immunity 58(4):889-908.e13 (2025).

3. Ichiyama K, Long J, Kobayashi Y, Horita Y, Kinoshita T, Nakamura Y, Kominami C, Georgopoulos K, Sakaguchi S. Transcription factor Ikzf1 associates with Foxp3 to repress gene expression in Treg cells and limit autoimmunity and anti-tumor immunity. Immunity 57(9):2043-2060. e10 (2024).

4. Kidani Y, Kitagawa Y, Hagiwara M, Kawashima A, Kanazawa T, Wada H, Uemura M, Nonomura N, Motooka D, Nakamura S, Ohkura N, Sakaguchi S. Down-regulation of TCF7 and LEF1 is a key determinant of tumor-infiltrating regulatory T cell function. Int Immunol. 36(4):167-182 (2024).

5. Yasumizu Y, Takeuchi D, Morimoto R, Takeshima Y, Okuno T, Kinoshita M, Morita T, Kato Y, Wang M, Motooka D, Okuzaki D, Nakamura Y, Mikami N, Arai M, Zhang X, Kumanogoh A, Mochizuki H, Ohkura N, Sakaguchi S. Single-cell transcriptome landscape of circulating $CD4^+$ T cell populations in autoimmune diseases. Cell Genom. 4(2):100473 (2024).

Malaria Immunology

Cevayir Coban, MD

Professor	Cevayir Coban
Associate Professor	Niloufar Kavian-Tessler
Assistant Professor	Jalal Alshaweesh
Postdoctoral Fellow	1
Research Assistant	2
Visiting Scientist	1
Support Staff	1

Our laboratory focuses on understanding the complex interactions between pathogens and the host immune system. While our initial efforts centered on malaria immunology, we have since broadened our scope to comprise viral infections and neglected parasitic diseases such as leishmaniasis. By dissecting the immune mechanisms underlying host responses to these diverse pathogens, we aim to discover effective vaccines and therapeutic strategies. Ultimately, our research aims to extend beyond infectious diseases towards broader immunological understanding and translational applications.

Chronic bone loss is an underappreciated sequela of malaria, with poorly defined mechanisms. We previously demonstrated that sustained accumulation of *Plasmodium* products in the bone marrow drives chronic inflammation in osteoblast (OB) and osteoclast (OC) precursors, promoting bone loss via MyD88-dependent manner (*Lee et al., Sci Immunol, 2017*). However, specific contribution of MyD88 in OB versus OC lineages remain unclear. To delineate the intrinsic function of MyD88 in bone homeostasis and malaria-induced pathology, we employed conditional MyD88 deletion in OB or OC lineages using the Lox-Cre system. MyD88-deficient OBs exhibited trabecular bone loss comparable to controls post-*Plasmodium yoelii*NL infection, whereas OC-specific MyD88 deletion significantly attenuated bone loss, implicating OC-intrinsic MyD88 in mediating inflammation-driven resorption (Figure). Unexpectedly, OB-specific MyD88 deletion under basal conditions resulted in reduced trabecular bone mass and impaired bone formation, associated with diminished systemic and local IGF-1 levels, suggesting a critical role for MyD88 in OB differentiation. Collectively, these findings reveal a dual role for MyD88: an essential intrinsic regulator of OB-mediated bone formation, and a partial mediator of OC-driven bone loss during malaria. These insights offer potential avenues for targeted intervention in malaria-associated and non-associated skeletal pathology (*Alshaweesh et al., Int Immunol, 2024*; Editor's choice article in September issue).

Cutaneous leishmaniasis (CL), a zoonotic parasitic disease, is increasingly reported in Mediterranean and European regions due to human migration and environmental changes. In Türkiye and other countries with high migrant influx, CL cases are emerging in non-endemic urban areas, where clinical unfamiliarity may lead to misdiagnosis. We retrospectively analyzed 12 CL cases diagnosed between 2013 and 2022 at a multi-provincial pathology center in Türkiye. Clinical data, initial diagnoses, histopathology, and molecular findings were evaluated. All patients presented with non-healing cutaneous lesions. CL was considered in the clinical differential in only 58.3% of cases; 50% were initially misdiagnosed as skin tumors, resulting in wide excisions in four cases. Histopathology revealed chronic or mixed inflammation dominated by histiocytes. PCR on tissues identified *Leishmania infantum* in 10 cases and *L. major* in two. All five tumor-misdiagnosed cases were caused by *L. infantum* and showed granulomatous inflammation. These findings show the diagnostic challenge of CL in non-endemic settings and emphasize the need for increased clinical awareness and molecular confirmation (*Ekemen et al., Front Med, 2024*).

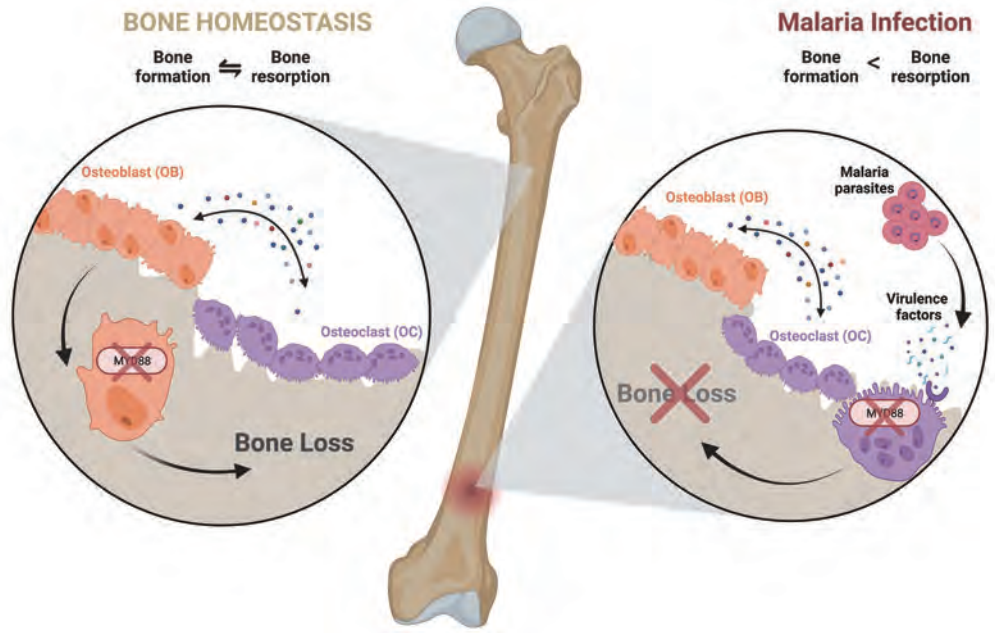

Figure.
MyD88 in osteoclast- and osteoblast-lineages differentially controls bone remodeling in homeostasis and malaria (*Alshaweesh et al., International Immunology, 2024*, * Editor's choice for September issue).

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1. Ekemen S, Nalcaci M, Toz S, Sanjoba C, Demirkesen C, Cetin ED, Tecimer T, Yildiz P, Gursel M, Ince U, Ozbel Y and Coban C. Diagnostic challenges in cutaneous leishmaniasis due to atypical Leishmania infantum: pathologists' insights from re-emergence zones. Frontiers in Medicine 11:1453211 (2024).

2. Alshaweesh J, Dash R, Lee MSJ, Kahyaoglu P, Erci E, Xu M, Matsuo-Dapaah J, Del Rosario Zorrilla C, Aykac K, Ekemen S, Kobiyama K, Ishii KJ, Coban C. MyD88 in osteoclast- and osteoblast-lineages differentially controls bone remodeling in homeostasis and malaria. Int Immunol. 36(9):451-464 (2024).

3. Lee MSJ, Matsuo Dapaah J, Del Rosario Zorrilla C, Omatsu Y, Nagasawa T, Uemura S, Iwama A, Ishii KJ, Coban C. Acute malaria suppresses the B lymphocytic niche in the bone marrow through the alteration of CXCL12-abundant reticular cells. Int Immunol. 36(7):339-352 (2024).

4. Lee MSJ, Inoue T, Ise W, Matsuo-Dapaah J, Wing JB, Temizoz B, Kobiyama K, Hayashi T, Patil A, Sakaguchi S, Simon AK, Bezbradica JS, Nagatoishi S, Tsumoto K, Inoue JI, Akira S, Kurosaki T, Ishii KJ, Coban C. B cell intrinsic TBK1 is essential for germinal center formation during infection and vaccination in mice. J Exp Med. 219(2):e20211336 (2022).

5. Coban C. The host targeting effect of chloroquine in malaria. Curr Opin Immunol.66:98-107 (2020).

Vaccine Science

Ken J. Ishii, MD/PhD

Professor	Ken J. Ishii
Associate Professor	Kouji Kobiyama
Assistant Professor	Burcu Temizoz
	Tomoya Hayashi
Postdoctoral Fellow	2
Visiting Scientist	4
Support Staff	8

Our laboratory investigates the immunological mechanisms driving intercellular and intracellular signaling pathways that mediate the immunogenicity of vaccines and biological responses to adjuvants. These insights aim to inform the rational development of next-generation vaccine platforms and immunotherapeutics targeting infectious diseases, cancers, allergies, and other non-communicable conditions.

STING Pathway Modulation: From Mouse-Specific Agonists to Human-Relevant Therapeutics

The stimulator of interferon genes (STING) pathway is a central mediator of innate immunity and a promising target for cancer immunotherapy and treatment of autoinflammatory disorders. DMXAA is a mouse-specific STING agonist that reached phase III clinical trials for lung cancer despite not fully activating human STING. Our findings revealed that DMXAA functions as a partial agonist in humans and can compete with full agonists, potentially explaining its limited efficacy and antagonistic effects in human contexts. This antagonism might be therapeutically beneficial, particularly in low-antigenicity lung tumors, where STING has been implicated in tumor progression.

To overcome DMXAA's species-specific limitations, we synthesized a novel xanthone derivative, HHMX (3-hydroxy-5-(4-hydroxybenzyl)-4-methyl-9H-xanthen-9-one). HHMX robustly antagonizes STING signaling across mouse and human systems. It effectively inhibited hyperactivation in cells harboring STING gain-of-function mutations seen in STING-associated vasculopathy with onset in infancy (SAVI). Importantly, HHMX decreased type I interferon production and downstream inflammatory markers in SAVI patient-derived PBMCs, and therapeutic benefit was confirmed in a SAVI mouse model, where HHMX treatment slowed disease progression and systemic inflammation. These findings establish HHMX as a promising broad-spectrum STING pathway antagonist, with translational potential in SAVI and related interferonopathies.

Microbial dysbiosis fuels STING-driven autoinflammation through cyclic dinucleotides

In collaboration with researchers from Turkey, the Netherlands, and Japan, we further investigated host-microbiota interactions in STING-driven inflammation, with a specific focus on the role of cyclic dinucleotides (CDNs). Using a SAVI knock-in mouse model (STING N153S), we discovered that animals with severe gastrointestinal symptoms exhibited gut microbial dysbiosis, particularly reduced short-chain fatty acid-producing bacteria and increased segmented filamentous bacteria. These mice showed high levels of both microbiota- and host-derived CDNs in feces and systemic circulation, suggesting microbial contributions to STING activation. Treatment with broad-spectrum antibiotics restored microbial balance and suppressed systemic inflammation, highlighting the therapeutic impact of modulating dysbiosis in STING-related diseases. Human data mirrored these findings: SAVI patients had significantly elevated plasma CDNs, with contributions from both microbial and endogenous cGAS-dependent sources.

In systemic lupus erythematosus (SLE), although total serum CDNs were not elevated compared to healthy controls, CDN levels correlated strongly with type I IFN scores and anti-dsDNA antibody titers, indicating STING pathway involvement in a subset of SLE patients. No such correlations were found in

rheumatoid arthritis (RA), supporting the specificity of the CDN-STING axis. Collectively, our findings support the concept that systemic CDNs act both as biomarkers and drivers of autoinflammation. The source of CDNs—microbiota versus host—may guide personalized therapeutic strategies, targeting the microbiome or innate immune sensors like cGAS/STING, depending on patient phenotype (Figure 1).

Immunological analysis of LC16m8 vaccine: preclinical and early clinical insights into mpox

In response to the 2022–2024 global mpox outbreak, we assessed the immunogenicity and safety of LC16m8, an attenuated vaccinia virus-based vaccine originally developed for smallpox. In mice, LC16m8 induced strong humoral responses, particularly against MPXV H3, A35, and M1R antigens, and enhanced germinal center B cell and follicular helper T cell development. CAST/EiJ mice showed reduced MPXV lung titers post-challenge, indicating protective efficacy. In humans, LC16m8 vaccination elicited neutralizing antibodies against multiple MPXV clades, suggesting cross-protection. In non-human primates, local lesions occurred without systemic adverse effects, supporting vaccine safety (Figure 2). These results offer promising preclinical and early clinical support for LC16m8 as a next-generation mpox vaccine. Further evaluation, particularly in naive and immunocompromised populations, is warranted to validate its broader utility.

The 100 Days Mission

Ken J. Ishii contributes to the 100 Days Mission through advisory roles in CEPI, IPPS, and G7 STEG. The goal is to ensure rapid deployment of safe and effective countermeasures—vaccines, diagnostics, and therapeutics—within 100 days of a future pandemic's emergence. Our lab's research supports this mission by advancing adjuvant science, platform technologies, and regulatory preparedness.

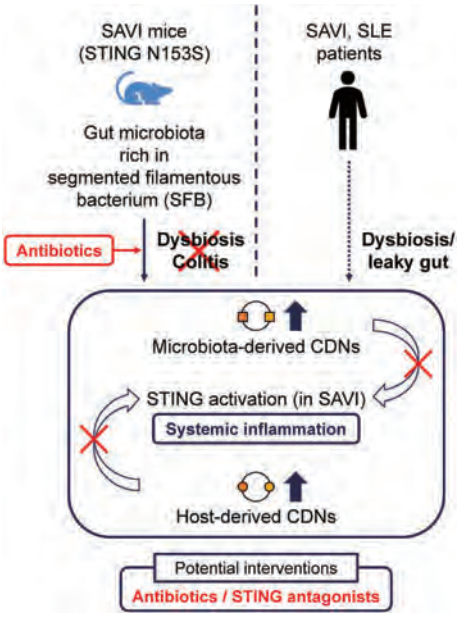

Figure 1.
Microbial and host-derived CDNs drive STING-mediated inflammation in SAVI and SLE.
SAVI mice with dysbiosis exhibit elevated fecal and systemic CDNs, leading to enhanced STING activation. Antibiotic treatment mitigates symptoms. Human SAVI and SLE patients with STING-driven subtypes show elevated CDNs, identifying these molecules as biomarkers and therapeutic targets.

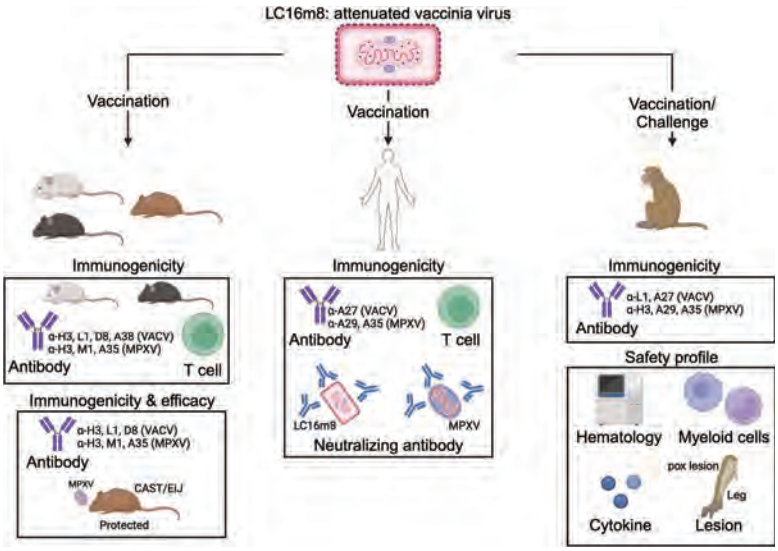

Figure 2.
LC16m8 Vaccine Induces Immune Responses Against Diverse Mpox Virus Strains.
LC16m8 induced strong antibody responses and cellular immunity in multiple mouse strains, and conferred protection against mpox virus infection. In humans, vaccinated individuals were confirmed to have developed neutralizing antibodies effective against various mpox virus strains.

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2. Kobiyama K, Utsumi D, Kaku Y, Sasaki E, Yasui F, Okamura T, Onodera T, Tobuse AJ, Sakkour A, Amiry AF, Hayashi T, Temizoz B, Liu K, Negishi H, Toyama-Sorimachi N, Kohara M, Sawasaki T, Takagi J, Sato K, Takahashi Y, Yasutomi Y, Ishii KJ. Immunological analysis of LC16m8 vaccine: preclinical and early clinical insights into mpox. EBioMedicine. 115:105703 (2025).

3. Temizoz B, Shibahara T, Hioki K, Hayashi T, Kobiyama K, Lee MSJ, Surucu N, Sag E, Kumanogoh A, Yamamoto M, Gursel M, Ozen S, Kuroda E, Coban C, Ishii KJ. 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a Partial STING Agonist, Competes for Human STING Activation. Front Immunol. 15:1353336 (2024).

4. Katsikis PD, Ishii KJ, Schliehe C. Challenges in developing personalized neoantigen cancer vaccines. Nat Rev Immunol. 24(3):213-227 (2024).

Immunoparasitology

Masahiro Yamamoto, PhD

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Research Assistant	2
Support Staff	2

Within a tumor mass, not only tumor cells but also various non-tumor cells, such as immune cells, fibroblasts, and vascular cells, are present, forming the so-called tumor microenvironment (TME). Some immune cells in the TME, such as cytotoxic $CD8^+$ T cells and natural killer cells, play anti-tumor roles, whereas others exhibit pro-tumor functions. Regulatory T cells (Tregs), a subset of helper $CD4^+$ T cells, play important roles in maintaining immune homeostasis and suppressing autoimmunity in healthy individuals. Among Tregs, a subset known as Th1-type Treg (Th1-Treg) highly accumulates within the tumor mass and suppresses anti-tumor immunity. Targeting Th1-Tregs for removal could be a promising cancer immunotherapeutic strategy, as it is considered safer than removing all Tregs, which could lead to autoimmunity. However, little is known about the molecular mechanisms that drive the high accumulation of Th1-Tregs in the TME.

Macrophages are innate immune cells present in various tissues, including the tumor microenvironment (TME), where they can differentiate into tumor-associated macrophages (TAMs), a specialized subset that plays a key role in promoting tumor growth and modulating immune responses. Since previous studies have shown that monoclonal antibody (mAb)-mediated macrophage depletion reduces Tregs in the TME, we questioned whether TAMs are involved in the increased presence of Th1-Tregs in the TME. To explore this potential causal relationship, we developed a novel transgenic mouse model in which TAMs can be specifically labeled and conditionally depleted using an intersectional genetic cell targeting system called VeDTR. We hypothesized that using these mice would enable us to analyze the impact of TAM depletion on the Th1-Treg population in the TME and reveal the cellular communication between TAMs and Tregs.

TAMs express arginase 1 (Arg1) at high and exclusive levels compared to other tissue-resident macrophages. When we selected the *Cx3cr1* and *Arg1* genes in the VeDTR system, $Arg1^+$ macrophages were specifically targeted in tumor-bearing mice. Using these mice, we found that $Arg1^+$ macrophages constitute a major subset of TAMs and were not detected in other organs. Upon depletion of $Arg1^+$ TAMs, we observed a reduction in both tumor growth and Th1-Treg ratios in the TME. We then examined whether $Arg1^+$ TAMs induce the polarization of Tregs into Th1-Tregs. Notably, co-culture with $Arg1^+$ TAMs induced Th1-Treg polarization, even without direct physical interaction. When we analyzed the humoral factors derived from Arg1+ TAMs that induce Th1-Treg polarization using single-cell and bulk RNA-seq analyses, we identified a chemokine called platelet factor 4 (PF4) as the inducer of Th1-Treg polarization, in a CXCR3-dependent manner. High PF4 expression in macrophages was detected specifically in $Arg1^+$ TAMs but not in other tissue macrophages. Additionally, we found that high concentrations of lactic acid, commonly associated with the "Warburg effect," might contribute to the induction of PF4 in macrophages. Both conventional and macrophage-specific PF4-deficient mice exhibited reduced tumor growth and Th1-Treg ratios in the TME. Finally, when we tested PF4 neutralization using a newly generated anti-PF4 mAb (#6-1-5) in tumor-bearing mice, both tumor growth and Th1-Treg ratios in the TME were reduced, leading to enhanced anti-tumor immunity.

We identified $Arg1^+$ TAM-secreted PF4 as a key determinant of Th1-Treg accumulation in the TME, which suppresses anti-tumor immunity and promotes tumor growth. Furthermore, PF4 neutralization inhibits Th1-Treg polarization and suppresses tumor growth. Given that data from The Cancer Genome Atlas

suggest that higher numbers of PF4^{+} TAMs are associated with poorer prognosis in humans, PF4 represents a potential new target for cancer immunotherapy.

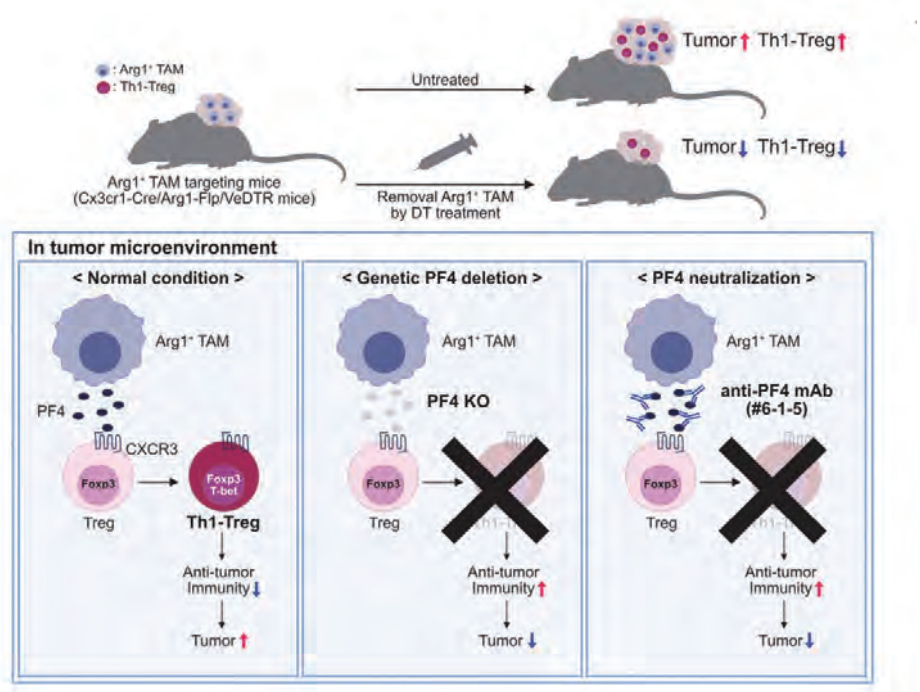

Figure.
Platelet factor 4-induced Th1-Treg polarization suppresses anti-tumor immunity.

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1. Kuratani A, Okamoto M, Kishida K, Okuzaki D, Sasai M, Sakaguchi S, Arase H, Yamamoto M. Platelet factor 4-induced TH1-Treg polarization suppresses antitumor immunity. Science 386:eadn8608 (2024).

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4. Okamoto M, Sasai M, Kuratani A, Okuzaki D, Arai M, Wing JB, Sakaguchi S, Yamamoto M. A genetic method specifically delineates Th1-type Treg cells and their roles in tumor immunity. Cell Rep. 42:e112813 (2023).

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Biochemistry & Immunology

Shigekazu Nagata, PhD

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Phospholipids are asymmetrically distributed in the plasma membrane bilayer (Sakuragi and Nagata, Nat. Rev. Mol. Cell Biol. 2023). Phosphatidylserine (PtdSer) and phosphatidylethanolamine (PtdEtn) localize to the inner leaflet, whereas phosphatidylcholine (PtdCho) and sphingomyelin (SM) are predominantly found in the outer leaflet. This asymmetry is maintained by flippases (P4-ATPases), which translocate PtdSer and PtdEtn to the inner leaflet using ATP.

Previously, we identified two P4-type ATPases, ATP11A and ATP11C, along with their subunit CDC50A, as flippases at plasma membranes (Segawa et al., Science 2014). Both ATPases selectively flip PtdSer, but not PtdCho, ensuring the asymmetric distribution of PtdSer. In 2021, we characterized a de novo point mutation (Q84E) in the exoplasmic domain of ATP11A found in a patient with neurological deterioration at Tohoku University Medical School (Segawa et al., J. Clin. Invest. 2021). This heterozygous dominant mutation alters the substrate specificity of ATP11A, enabling it to flip PtdCho in addition to PtdSer. The aberrant flipping of PtdCho resulted in a marked increase in SM concentrations in the outer leaflet, likely as a compensatory response to the inward translocation of PtdCho.

In collaboration with scientists in Canada, the USA, Belgium, and Hungary, we have now identified two additional point mutations (E114G and S399L) in the cytoplasmic region of ATP11A in three patients with a similar neurological disorder (Calianese et al., Proc. Nat. Acad. Sci. 2024). Molecular dynamics simulations suggest that these mutations enhance ATP11A's affinity for PtdCho. These findings underscore the critical role of the well-conserved entry and exit sites of flippases in determining phospholipid substrate specificity and indicate that aberrant PtdCho flipping contributes to neurological disorders.

The asymmetric distribution of phospholipids is disrupted during cell death processes such as apoptosis, necroptosis, and ATP-induced necrosis. In apoptotic cells, exposed PtdSer functions as an "eat me" signal, facilitating phagocytosis by directly binding to PtdSer receptors on phagocytes or indirectly through bridging molecules. The engulfment of apoptotic cells suppresses immune responses by inhibiting IFN-α/β and TNF production while promoting TGF-β and IL-10 secretion.

Although ATP11A and ATP11C flippases are inactivated by caspase-mediated cleavage, this alone is insufficient for rapid PtdSer exposure due to the high energetic barrier of spontaneous phospholipid movement across the membrane's hydrophobic core. Instead, scramblases, which nonspecifically and bidirectionally translocate phospholipids, are required.

We previously identified two scramblases, TMEM16F and XKR8, activated by calcium and caspases, respectively (Suzuki et al., Nature 2010; Science 2013). The XKR family also includes XK, which mediates PtdSer exposure during ATP-induced necrosis (Ryoden et al., Proc. Nat. Acad. Sci. 2022). Notably, apoptotic cells lacking XKR8 fail to expose PtdSer and are inefficiently engulfed by macrophages. Consequently, *Xkr8*-deficient mice develop systemic lupus erythematosus (SLE)-like autoimmunity or male infertility (Kawano et al., Proc. Nat. Acad. Sci. 2018).

Cryo-electron microscopy (cryo-EM) structural analysis of human XKR8 revealed an arrangement of eight transmembrane helices and two additional helices that partially penetrate the membrane (Sakuragi et al., Nat. Struct. Mol. Biol. 2023). Mutational analysis identified key structural features, including a hydrophobic cleft on the lipid-exposed surface for phospholipid recruitment, an intramolecular path of hydrophilic residues for phospholipid translocation, and a crucial tryptophan at the extracellular end

regulating scrambling activity. Recently, we reconstituted purified XKR8 in a nanodisc and determined its structure (Sakuragi et al., J. Biol. Chem. 2024). This analysis revealed that a cytoplasmic groove interacts with the C-terminal tail via polar and van der Waals forces. Caspase-mediated cleavage or phosphorylation appears to disrupt these interactions, potentially opening the path for phospholipid scrambling.

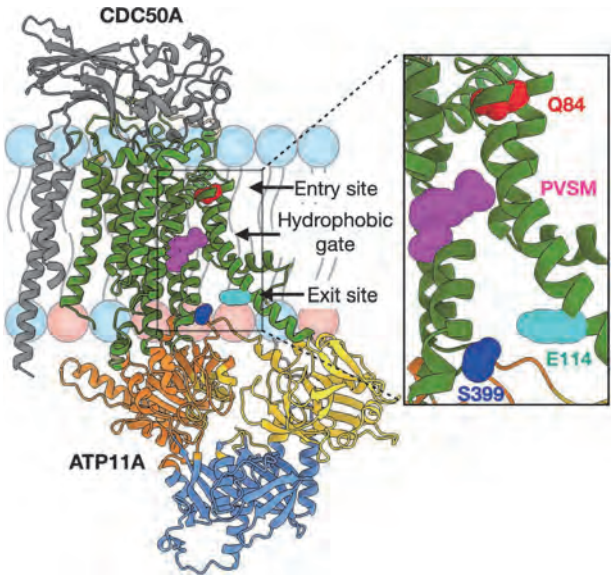

Figure 1.
Gain-of-function de novo ATP11A mutations identified in patients with neurological disorders
The ATP11A-CDC50A complex with the substrate entry/exit sites and the hydrophobic gate. PVSM residues form the hydrophobic gate. Q84 (red) is located at the entry site, while E114 (cyan) and S399 (blue) are at the exit site.

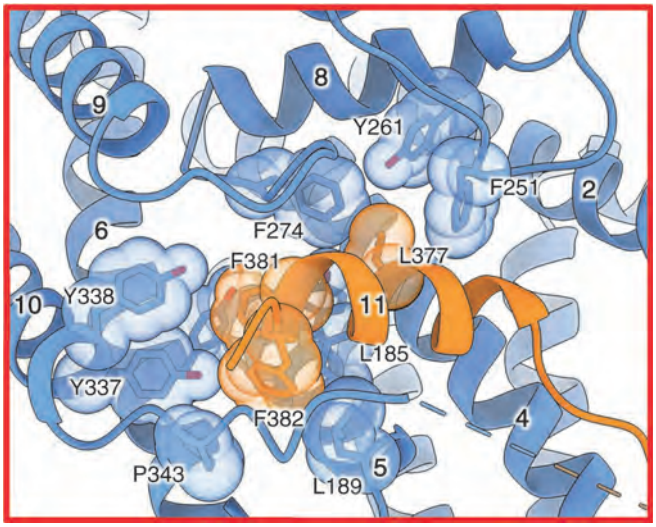

Figure 2.
The structure of the XKR8–basigin (BSG) complex.
The XKR8-BSG complex is viewed from the bottom. The helix 11 of XKR8 is shown in orange. Residues involved in the interaction are shown as a stick model or a sphere model.

Recent Publications

1. Chen XW, Don AS, Fedorova M, et al. Time for lipid cell biology, Nat Cell Biol. 27:169-174 (2025).

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Molecular Neuroscience

Toshihide Yamashita, MD/PhD

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Disorders of the central nervous system, such as cerebrovascular diseases, cerebrospinal trauma, and encephalomyelitis, often cause spatiotemporal changes in the nervous system and in various biological systems, such as the immune system and vascular system. We have analyzed disorders of the neural networks in the central nervous system and the subsequent restoration process from the perspective of the functional network of biological systems (Fig. 1). Further, we have analyzed the mechanism by which the spatiotemporal dynamics in those biological systems control a series of processes (Fig. 2). Particularly, the ultimate goal of this study is to elucidate the manner in which the control mechanism is affected by the associations among the nervous system, immune system, and vascular system. Additionally, we aim to elucidate the processes involved in the functioning of living organisms with neural network disorders within the central nervous system by observing such disorders and their functional recovery process with respect to the dynamics of the entire biological system and by conducting a comprehensive analysis of the association between each system.

We observe the central nervous system as a single organ within a biological system. Further, studies from the perspective of how the entire biological system is involved in disorders and recovery of neural networks are scarce. By observing disorders in neural networks and the biological reactions during the subsequent recovery process as a "scrap-and-build" strategy, we aim to elucidate the mechanisms behind a series of reactions as well as their significance that may potentially lead to a new and original trend in Life Sciences.

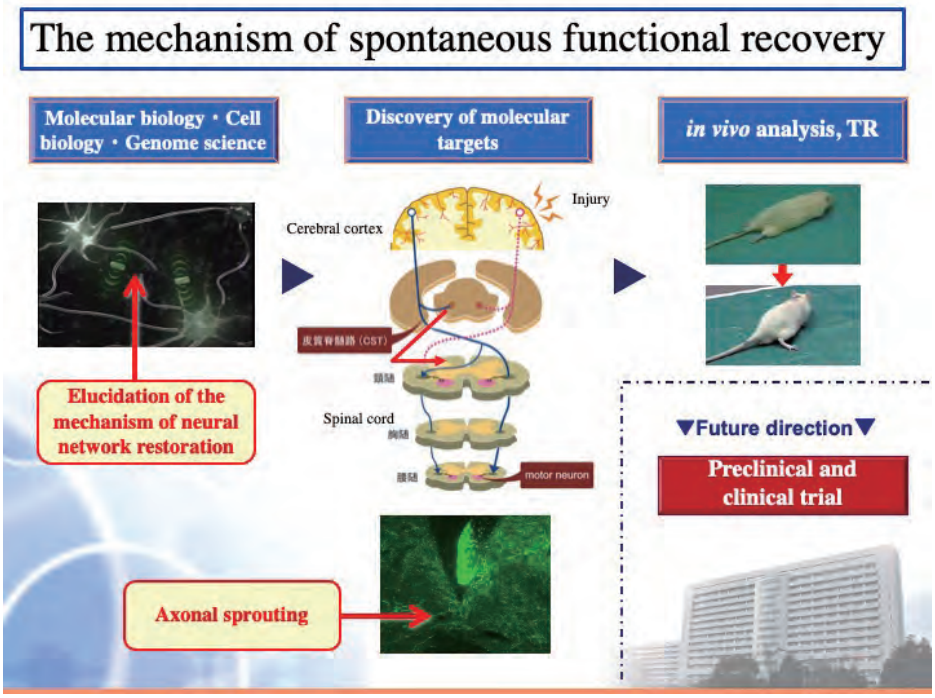

Figure 1.
The mechanism of spontaneous functional recovery.

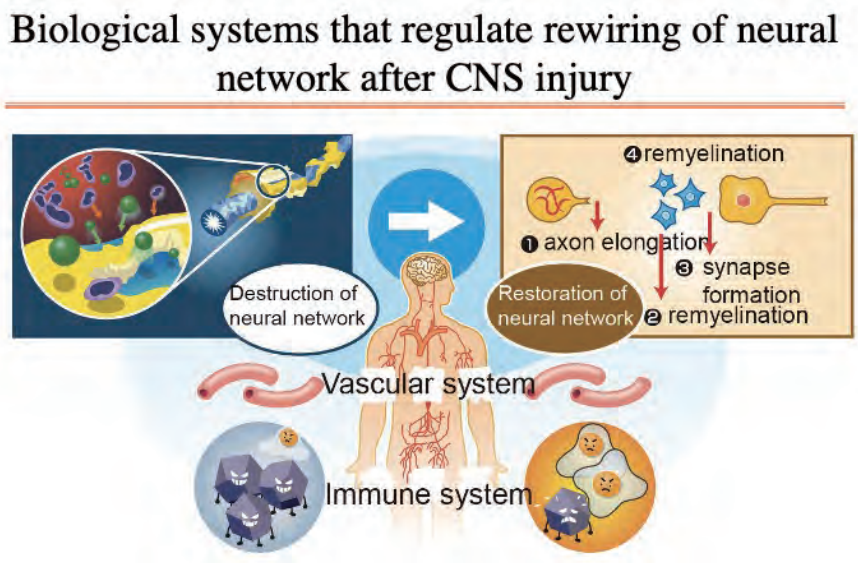

Figure 2.
Biological systems that regulate rewiring of neural network after CNS injury.

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1. Shimizu M, Shiraishi N, Tada S, Sasaki T, Beck G, et al. RGMa collapses the neuronal actin barrier against disease-implicated protein and exacerbates ALS. Sci. Adv. 9, eadg3193 (2023).
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Molecular Immunology

Sho Yamasaki, PhD

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Postdoctoral Fellow	5
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A conserved human CD4$^+$ T cell subset recognizing the mycobacterial adjuvant, trehalose monomycolate

As mycobacteria are protected by a thick lipid cell wall, humans have developed immune responses against diverse mycobacterial lipids. Many of these immunostimulatory lipids are known as adjuvants which act through innate immune receptors, such as C-type lectin receptors. While a few mycobacterial lipid antigens are known to activate unconventional T cells, the antigenicity of most adjuvant lipids remain unclear.

Recently, we identified that trehalose monomycolate (TMM), an abundant mycobacterial adjuvant, activates human T cells bearing a unique αβTCR. This recognition was restricted by CD1b, a monomorphic antigen presenting molecule conserved in primates. Single-cell TCR-RNA sequencing using newly established CD1b-TMM tetramers revealed that TMM-specific T cells are CD4$^+$ effector memory T cells in the periphery blood of healthy donors. Upon TMM stimulation, these cells express IFNγ, TNF and other anti-mycobacterial effectors. TMM-specific T cells were detected not only in the peripheral blood of healthy individuals from different ethnic backgrounds but also in cord blood. Their numbers were increased in the blood of active TB patients. Although TCR sequences of TMM-specific T cells were diverse, TRBV usage was skewed to TRBV4-1 and TRBV6-2 and CDR3 shared unique characteristics. Cryo-EM ternary complex revealed that these TCR features are crucial for recognizing TMM presented by CD1b.

TMM can simultaneously activate both innate and adaptive immunity. CD1b-restricted unconventional T cells have the advantage of being activated by the same antigen, regardless of individual MHC haplotypes. Therefore, TMM may be effectively utilized in TB vaccines through a novel mechanism distinct from previously known adjuvant modes of action.

Identification of alpha-galactosylceramide as an endogenous mammalian antigen for iNKT cells

Invariant natural killer T (iNKT) cells are unconventional T cells which express a fixed T cell receptor and recognize lipid antigens presented on CD1d. The most potent iNKT antigen is α-galactosylceramide (α-GalCer) which was originally identified from marine sponges. However, its presence in mammals has yet to be conclusively demonstrated. Ectopic expression of CD1d by melanoma cells can activate iNKT cells without additional antigens. NKT cell activation was decreased when serum was reduced, suggesting the source of the activating ligands. To investigate the activating ligands in serum, we developed an activation-based purification and a supercritical fluid chromatography tandem mass spectroscopy (SFC/MS/MS) method to distinguish the four hexosylceramide diastereomers, and α-GalCer was identified. Furthermore, the same SFC/MS/MS method was used to identify α-GalCer from bile and immune organs. This study shows the first evidence that α-GalCer is present in mammals.

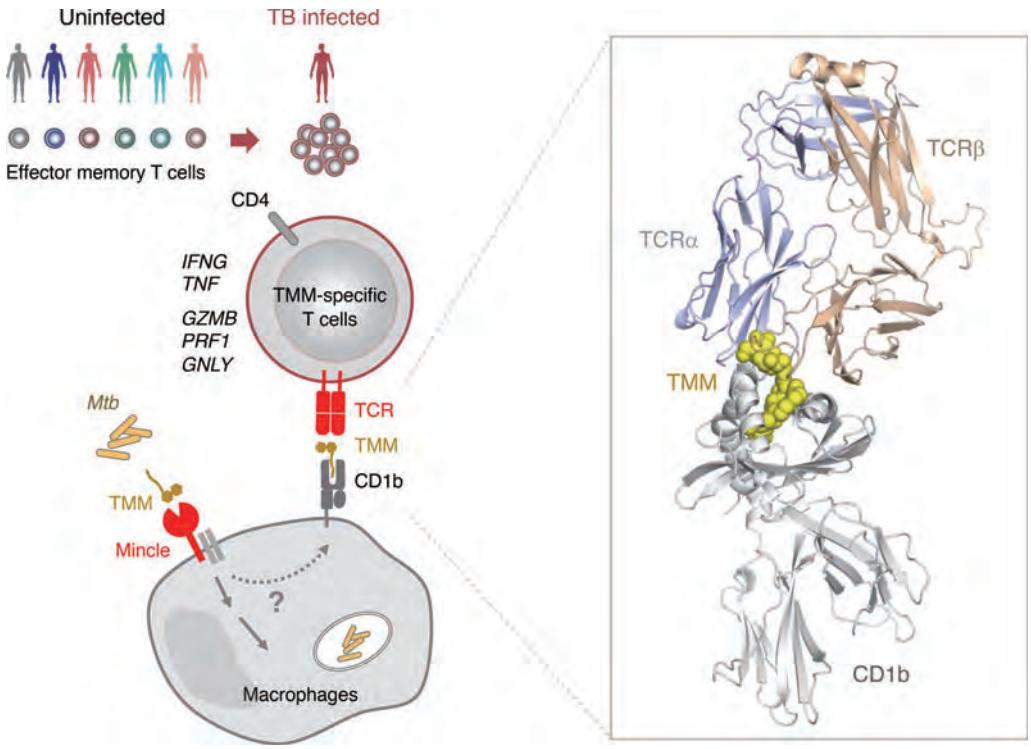

Figure.
T cells specifically recognizing TMM by a TCRαβ with unique features are conserved among individuals and may contribute to infection defense.

Recent Publications

1. Hosono Y, Tomiyasu N, Kasai H, Ishikawa E, Takahashi M, Imamura A, Ishida H, Compostella F, Kida H, Kumanogoh A, Bamba T, Izumi Y, Yamasaki S. Identification of α-galactosylceramide as an endogenous mammalian antigen for iNKT cells. J Exp Med. 222(2):e20240728 (2025).

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3. Takeuchi Y, Ishikawa E, Sato T, Shinkai M, Takahashi Y, Lu X, Yamasaki S. Analysis of antigen specificity of Treg cell clonotypes expanded upon SARS-CoV-2 infection. Int Immunol. dxae072 (2024).

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5. Reis E Sousa C, Yamasaki S, Brown GD. Myeloid C-type lectin receptors in innate immune recognition. Immunity 57(4):700-717 (2024).

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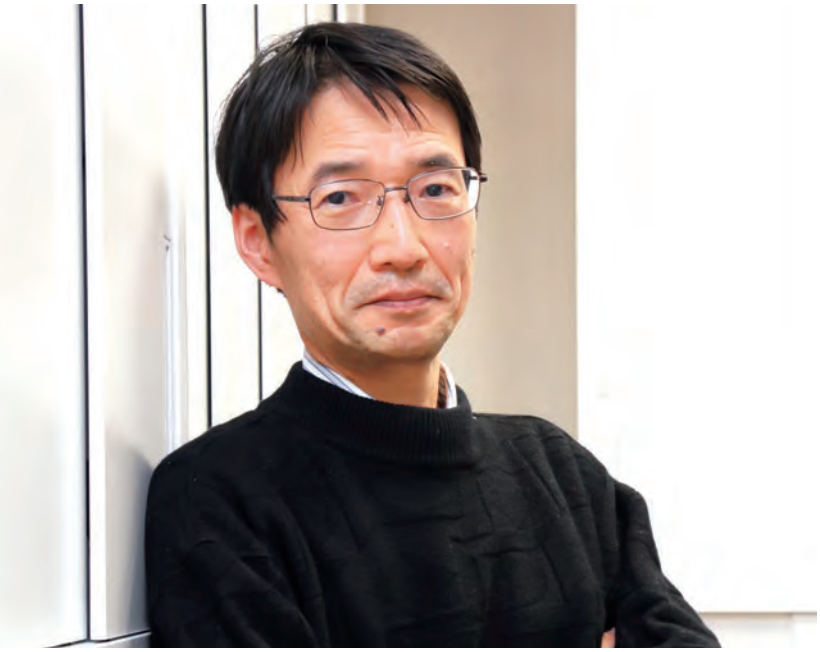
Stem Cell Biology and Developmental Immunology



Takashi Nagasawa, MD/PhD

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Specialized microenvironments known as niches are essential for the maintenance of hematopoietic stem cells (HSCs), which give rise to most blood cells, supporting lympho-hematopoiesis within the bone marrow (BM). We isolated the chemokine CXCL12 (also known as SDF-1 or PBSF) (Nagasawa et al., *PNAS* 1994) and found that CXCL12 and its receptor CXCR4 are essential for BM colonization by HSCs during embryogenesis (Nagasawa et al., *Nature* 1996; Ara et al., *Immunity* 2003), maintaining the HSC pool (Sugiyama et al., *Immunity* 2006), and for the development of immune cells, including B cells, plasmacytoid dendritic cells, and NK cells as well as vascular formation and cardiogenesis (Tachibana et al., *Nature* 1998).

Based on the pivotal role of CXCL12 in HSC maintenance, we identified a population of cells expressing high levels of CXCL12 within the BM, which we termed CXCL12-abundant reticular (CAR) cells. We found that BM-CAR cells are the major producers of CXCL12 and SCF, and represent major cellular components of niches for HSCs and immune cells, including B cells and plasma cells (Tokoyoda et al., *Immunity* 2004; Sugiyama et al., *Immunity* 2006; Omatsu at al., *Immunity* 2010). Leptin receptor-expressing ($LepR^+$) cells show strong overlap with CAR cells (Ding et al., *Nature* 2012). We further confirmed that CXCL12 produced by BM-CAR cells is essential for the maintenance of HSCs and lympho-hematopoiesis (Nakatani et al., *Nat Commun* 2023). Moreover, we showed that numerous HSC niches remain unoccupied and that all BM-CAR cells can serve as facultative niches for HSCs, challenging the classical model of niche occupancy (Shimoto et al., *Blood* 2017).

Concerning the nature of BM-CAR cells, we demonstrated that they are mesenchymal stem cells capable of differentiating into adipocytes and osteoblasts. We also found that the transcription factors Foxc1 and Ebf3 are preferentially expressed in BM-CAR cells and play critical roles in HSC niche formation and maintenance by inhibiting their differentiation into adipocytes and osteoblasts, respectively (Omatsu et al., *Nature* 2014; Seike et al., *Genes Dev*. 2018). Furthermore, we showed that BM-CAR cells require Runx1 or Runx2 to prevent fibrotic conversion and to maintain HSCs and hematopoiesis in adult BM (Omatsu et al., *Nat Commun* 2022) (Figure 1). In addition to our findings in mice, we identified the human counterpart of CAR cells, which specifically express CXCL12, Foxc1, and Ebf3, and constitute the major population of non-hematopoietic cells in human BM (Aoki et al., *Br J Haematol* 2021).

Universal fibroblasts from the lung and the colon outside the skeletal system and muscle can give rise to BM-CAR cells

Fibroblasts are non-hematopoietic, non-endothelial, non-epithelial, and non-parenchymal cells that secrete structural and signaling molecules. They have traditionally been considered structural components of organs and connective tissues. However, we have shown that BM-CAR cells constitute a fibroblast population characterized by salient features, including high expression of CXCL12 and the transcription factors Foxc1 and Ebf3, and function as HSC niche cells as described above. On the other hand, in the intestine a population of fibroblasts known as $Foxl1^+$ telocytes has been shown to specifically express the transcription factors Foxl1 and Sox6 and to be essential for maintaining intestinal stem cells (Shoshkes-Camel et al *Nature* 557; 242, 2018). The similarities in morphology and function

between BM-CAR cells and Foxl1$^+$ telocytes raise the possibility that both may originate from a common progenitor. A recent meta-analysis of 28 single-cell RNA sequencing (scRNA-seq) datasets, encompassing approximately 120,000 fibroblasts from 16 tissues, identified a population of fibroblasts expressing high levels of a proteoglycan, Dpt and Pi16 that are present in all tissues. These cells were termed universal fibroblasts, and it was hypothesized that they give rise to distinct, tissue-specific fibroblast subsets, termed specialized fibroblasts, such as BM-CAR cells, Foxl1$^+$ telocytes, and splenic red pulp fibroblasts (Buechler et al.. *Nature* 593; 575, 2021). However, direct *in vitro* and *in vivo* evidence supporting the concept of fibroblasts has been lacking. To obtain direct evidence, we investigated the *in vivo* potential of universal fibroblasts from various postnatal tissues to differentiate into the specialized BM fibroblasts, specifically CAR cells.

We isolated GFP$^+$PDGFRα$^+$Sca-1$^+$CD34$^+$CD45$^-$Ter119$^-$CD31$^-$ universal fibroblasts from the lung, colon, and muscle of Ubc-GFP;CXCL12-tdTomato mice using flow cytometry. These cells expressed high levels of the universal fibroblast marker Dpt, but not CXCL12, SCF, Foxc1, Ebf3, or Runx1. They were then suspended in Matrigel supplemented with BMP2 and implanted into the tibialis anterior muscle of wild-type recipient mice. Eight weeks after transplantation, we observed ectopic bone formation containing bone marrow, where donor-derived GFP$^+$PDGFRβ$^+$CD45$^-$Ter119$^-$CD31$^-$ cells expressed CXCL12-tdTomato at levels comparable to BM-CAR cells (Figure 2). These cells also expressed higher levels of the other HSC-niche factors, including CXCL12, SCF, Foxc1, Ebf3, and Runx1, compared with universal fibroblasts and other cell populations, and were capable of supporting HSC maintenance *in vitro*.

We next isolated GFP$^+$ universal fibroblasts from the lung, colon, and muscle of Ubc-GFP;CXCL12-tdTomato mice and injected them into the bone marrow of lethally irradiated recipient mice. In these recipients, we detected donor-derived GFP$^+$ cells that expressed CXCL12-tdTomato at levels comparable to CAR cells and showed higher expression of other HSC-niche factors, including Foxc1 and Ebf3, than other BM populations. These results demonstrate that universal fibroblasts capable of differentiating into BM-specific HSC niche cells (CAR cells) are distributed throughout the body, providing a valuable starting point for elucidating fibroblastic cell lineage relationships and the nature of tissue stem cell niches (Figure 3).

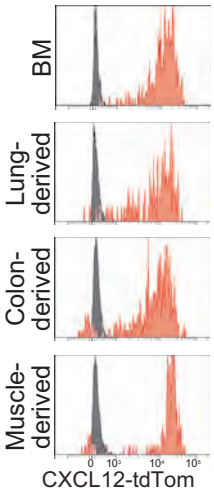

Figure 2.
Universal fibroblasts from various tissues give rise to CXCL12-expressing cells during ectopic bone formation.
Flow cytometric analysis of CXCL12-tdTomato expression in Ubc-GFP$^-$ (gray) and Ubc-GFP$^+$ (red) subsets of PDGFRβ$^+$CD45$^-$Ter119$^-$CD31$^-$ cells isolated from the ectopic bones formed by transplantation of universal fibroblasts from the lung, colon, and muscle of CXCL12-tdTomato mice.

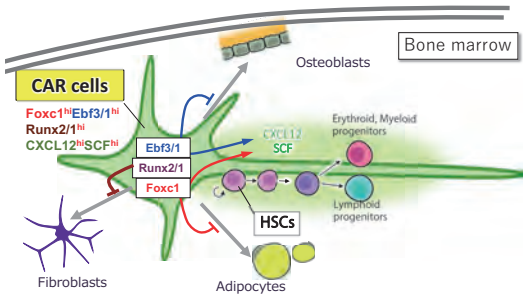

Figure 1.
The functions of BM-CAR cells.
CAR cells are the major cellular component of HSC niches in both mouse and human bone marrow. They preferentially express the transcription factors Foxc1, Ebf1/Ebf3, and Runx1/2 as well as the cytokines CXCL12 and SCF, all of which are essential for the formation and maintenance of niches that support HSCs and immune cells.

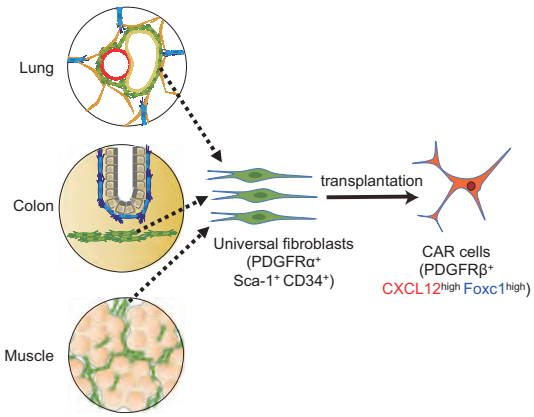

Figure 3.
Universal fibroblasts from various tissues have potential to give rise to BM-CAR cells.
Universal fibroblasts isolated from the lung, colon, and muscle differentiated in vivo into CAR cells.

Recent Publications

1. Higaki K, Aiba S, Shimoyama T, Omatsu Y, Nagasawa T. Universal fibroblasts across tissues can differentiate into niche cells for hematopoietic stem cells. Cell Rep. in press.
2. Nakatani T, Sugiyama T, Omatsu Y, Watanabe H, Kondoh G, Nagasawa T. Ebf3$^+$ niche-derived CXCL12 is required for the localization and maintenance of hematopoietic stem cells. Nat Commun. 14(1):6402 (2023).
3. Omatsu Y, et al. Runx1 and Runx2 inhibit fibrotic conversion of cellular niches for hematopoietic stem cells. Nat Commun. 13(1):2654 (2022).
4. Seike M, et al. Stem cell niche-specific Ebf3 maintains the bone marrow cavity. Genes Dev. 32(5-6); 359-372 (2018).
5. Omatsu Y, et al. Foxc1 is a critical regulator of haematopoietic stem/progenitor cell niche formation. Nature 508: 536-540 (2014).
6. Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 25:977-988 (2006).

Aging Biology

Eiji Hara, PhD

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Support Staff	2

We all experience aging, a phenomenon in which our biological functions deteriorate. We all want to avoid aging because it leads to a decline in quality of life and the development of severe age-related diseases such as cancer and dementia. Therefore, research has been conducted in many countries with aging populations, including Japan, to extend a healthy life span by slowing the aging process. Recently, it has become clear that one of the causes of aging is the increase of senescent cells, which accumulate in the body with age and secrete various inflammatory substances, thereby accelerating the aging process. However, it remains unclear why and how senescent cells accumulate in the body with aging, and how this accumulation contributes to aging and/or aging-associated diseases.

In recent years, there has been increasing attention towards understanding the relationship between age-related alterations in the oral microbiota and age-associated diseases, with reports emphasizing the significance of maintaining a balanced oral microbiota for host health. However, the precise mechanisms underlying age-related changes in the oral microbiota remain elusive. We recently reported that cellular senescence of ileal germinal center (GC) B cells, triggered by the persistent presence of commensal bacteria, results in diminished IgA production with aging and subsequent alterations in the gut microbiota. Consequently, we hypothesize that a similar phenomenon may occur in the oral cavity, potentially contributing to age-related changes in the oral microbiota. Examination of *p16-luc* mice, wherein the expression of the senescent cell marker $p16^{INK4a}$ can be visualized, raised under specific pathogen-free (SPF) or germ-free (GF) conditions, indicated that, unlike ileal GC B cells, the accumulation of senescent cells in GC B cells of cervical lymph nodes increases with age regardless of the presence of commensal bacteria. Furthermore, longitudinal studies utilizing the same individual mice throughout their lifespan revealed concurrent age-related alterations in the composition of the oral microbiota and a decline in salivary IgA secretion. Further investigation involving $Rag1^{-/-}$ mice transplanted with B cells from wild-type or $p16^{INK4a}$-knockout mice unveiled that B cell senescence leads to reduced IgA secretion and alteration of the oral microbiota. This study elucidated that cellular senescence of GC B cells occurs in cervical lymph nodes with aging, resulting in reduced salivary IgA secretion and influencing age-related alterations in the oral microbiota. These findings advance our understanding of the mechanism of age-associated changes in the oral microbiota and open up possibilities of their control.

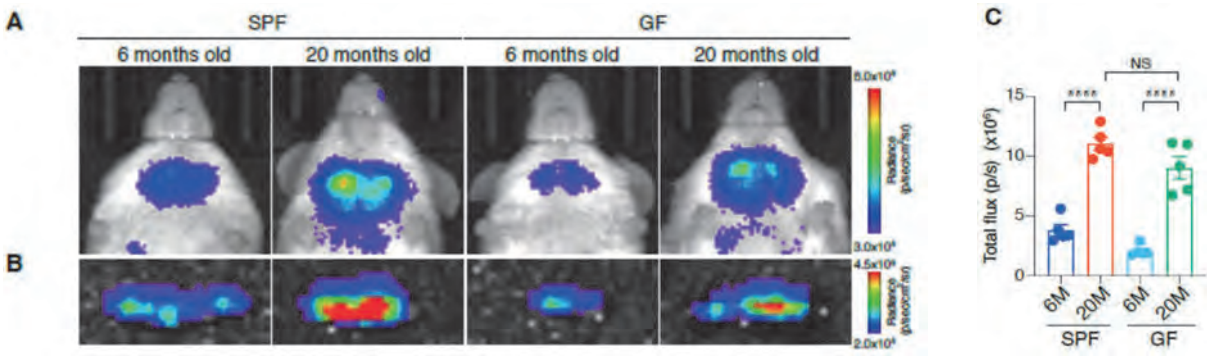


Figure 1

Bacteria-independent induction of p16^{INK4a} expression in cervical lymph nodes with aging.
Representative images of non-invasive BLI **(A)** or ex vivo BLI of cervical lymph nodes **(B)** of *p16-luc* mice raised in SPF or GF environment. The color bars indicate the radiance with minimum and maximum threshold values. **C**, The bioluminescence intensity emitted from the cervical lymph nodes.

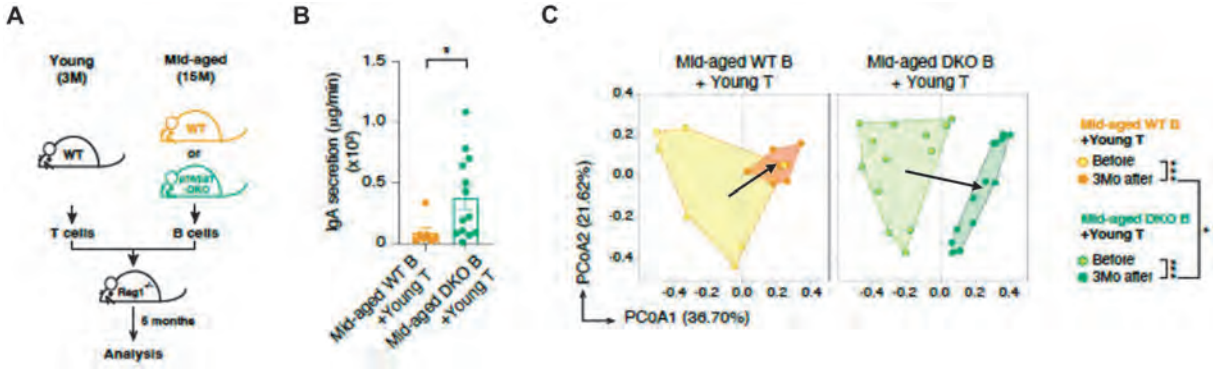


Figure 2.

Age-related changes in B cells cause dysregulation of the oral microbiota by altering IgA secretion in saliva.
T cells isolated from young (3M) WT mice together with B cells isolated from mid-aged (15M) WT or p16/p21-DKO mice were transplanted into *Rag1–/–* mice and analyzed five months after transplantation. Experimental schemes for T- and B-cell reconstitution models using *Rag1–/–* mice are shown **(A)**. Transplanted mice were examined for IgA secretion in saliva **(B)** and comparison of oral microbiota composition before and after T and B cell reconstitution **(C)**. Principal Coordinate Analysis (PCoA) plots of the Bray-Curtis distance show changes in oral bacterial composition before and after T and B cell reconstitution.

Recent Publications

1. Mizuno H, et al. B cell senescence promotes age-related changes in oral microbiota. Aging Cell. 23:e14304 (2024).
2. Kawamoto S, et al. Bacterial induction of B-cell senescence promotes age-related changes in the gut microbiota. Nat Cell Biol. 25:865-876 (2023).
3. Tsuji S, et al. SARS-CoV-2 infection triggers paracrine senescence and leads to a sustained senescence-associated inflammatory response. Nat Aging 2:115-124 (2022).
4. Okumura S, et al. Gut bacteria identified in colorectal cancer patients promote tumourigenesis via butyrate secretion. Nat Commun. 12:5674 (2021).

Signal Transduction

Nobuyuki Takakura, MD/PhD

Professor	Nobuyuki Takakura
Assistant Professor	Fumitaka Muramatsu Weizhen Jia Bal Zeynep Keigo Akuta Fitriana N. Rahmawati
Postdoctoral Fellow	1
Research Assistant	7
Support Staff	2

Blood vessel formation is essential for organogenesis and organ integrity. Process of blood vessel is divided into two mechanisms. One is vasculogenesis, a do novo blood vessel formation usually observed in embryos. In this process, mesodermal cells differentiate into endothelial cells (ECs) and ECs form tube. Mural cells are recruited near ECs and adhere to ECs for the structural stabilization. After birth, new blood vessels are usually developed from preexisting blood vessels by the sprouting angiogenesis. There are more than three types of ECs for sprouting angiogenesis. Initially, tip ECs emerge for the guidance of migration direction of new branch. This cell type does not have ability to proliferate. Beneath tip ECs, stalk ECs adhere and they have ability to generate a large number of ECs for elongation of new branch. Finally, phalanx ECs emerge to induce maturation of new blood vessels by cell-cell adhesion through VE-cadherin. Moreover, ECs from arteries, veins and capillaries are genetically different. These suggest that ECs have heterogeneity; however, how such heterogeneity of ECs is induced has not been elucidated.

We hypothesized that endothelial stem cells exist in pre-existing blood vessels, maintaining an undifferentiated state under steady-state condition. Upon tissue hypoxia and inflammation, these cells produce endothelial progenitors with a high proliferative capacity for ECs. We fractionated ECs from pre-existing blood vessels based on their ability to efflux drugs (Hoechst, a DNA dye) from inside the cells to the outside. Our finding show that ECs expressing ABC transporters, such as ABCG2, include those with a highly proliferative ability. We isolated CD157 and CD200 as specific cell surface markers expressed on these ECs, and lineage tracing analysis revealed that $CD157^{+}CD200^{+}$ ECs differentiate into $CD157^{-}CD200^{+}$ endothelial progenitors, which produce a large number of ECs. Furthermore, in the liver, these $CD157^{-}CD200^{+}$ ECs eventually differentiate into $CD157^{-}CD200^{-}$ ECs, which lose their proliferative ability. Therefore, we concluded that $CD157^{+}CD200^{+}$ ECs are endothelial stem cells, and there exists a hierarchy of differentiation within the EC system.

Organ-specific somatic stem cells have been identified in hematopoietic cells, neuronal cells, gut epithelium, and skin cells, and their importance for tissue regeneration has been suggested. The biological significance of endothelial stem cells should also be addressed. Therefore, we observed the development and differentiation of endothelial stem cells from embryo to adult by analyzing genotype and phenotype using scRNA sequencing and flow cytometry (Figure). The results suggest that there are no endothelial stem cells, but only $CD157^{-}CD200^{-}$ ECs during early embryogenesis. However, we found that $CD157^{-}CD200^{+}$ endothelial progenitors emerged from $CD157^{-}CD200^{-}$ ECs around perinatal period, and subsequently, $CD157^{+}CD200^{+}$ endothelial stem cells appeared after birth and proliferated. These findings suggested that vascular endothelial development occurs in two waves: in the early embryo, non-endothelial stem cells/progenitors generate monotonous primary vascular plexus, and endothelial stem cells emerge to generate tissue/organ specific vascular systems (Nahmawati et al. Exp Hematol). It is interesting to compare hematopoiesis with vascular development, as there are similarities between these two systems.

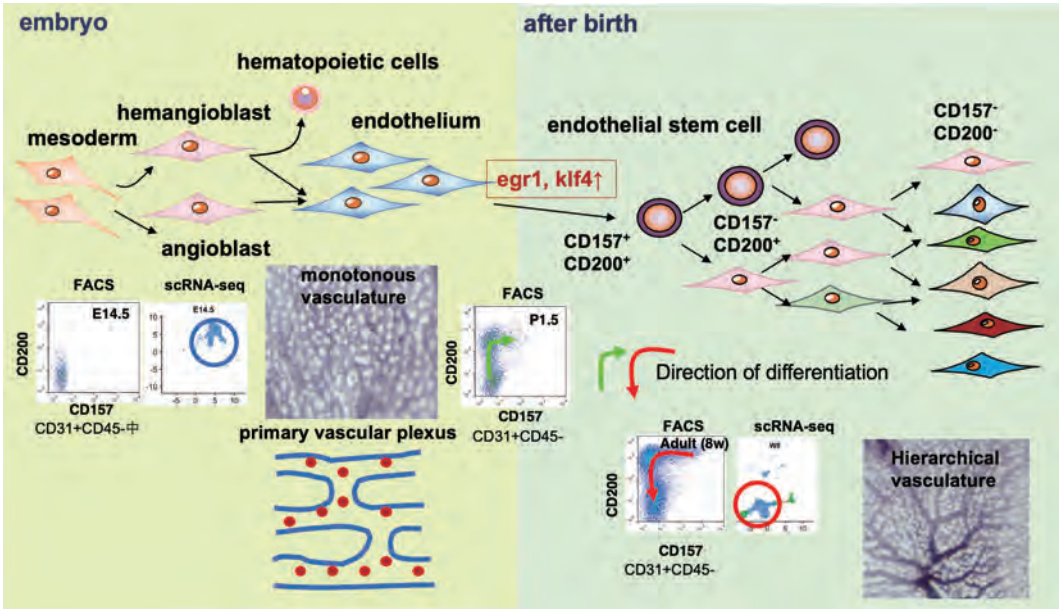


Figure.

Endothelial stem cell population may regulate organ-specific vascularity after birth.

The genotype of endothelial cells (ECs), analyzed by single-cell RNA sequencing, was compared to the cell surface phenotype, analyzed by flow cytometry. $CD157^{+}CD200^{+}$ endothelial stem cells emerge around the perinatal period and differentiate into $CD157^{-}CD200^{-}$ terminally differentiated ECs through $CD157^{-}CD200^{+}$endothelial progenitors. During early embryogenesis, ECs do not express endothelial specific markers, but these EC may give rise to endothelial stem cells through gene modification, possibly mediated by transcription factors such as Egr1 and Klf4.

Recent Publications

1. Matsui Y, Muramatsu F, Nakamura H, Noda Y, Matsumoto K, Kishima H, Takakura N. Brain-derived endothelial cells are neuroprotective in a chronic cerebral hypoperfusion mouse model. Commun Biol. 7:338 (2024).

2. Jia W, Kong L, Kidoya H, Naito H, Muramatsu F, Hayashi Y, Hsieh HY, Yamakawa D, Hsu DK, Liu F-T, and Takakura N. Indispensable role of Galectin-3 in promoting quiescence of hematopoietic stem cells. Nature Commun. 12:2118 (2021).

3. Kidoya H, Muramatsu F, Shimamura T, Jia W, Satoh T, Hayashi Y, Naito H, Kunisaki Y, Arai F, Seki M, Suzuki Y, Osawa T, Akira S, Takakura N. Regnase-1-mediated post-transcriptional regulation is essential for hematopoietic stem and progenitor cell homeostasis. Nat Commun. 10:1072 (2019).

4. Naito H, Iba T, Wakabayashi T, Tai-Nagara I, Suehiro JI, Jia W, Eino D, Sakimoto S, Muramatsu F, Kidoya H, Sakurai H, Satoh T, Akira S, Kubota Y, Takakura N. TAK1 prevents endothelial apoptosis and maintains vascular integrity. Dev Cell 48:151-166 (2019).

5. Wakabayashi T, Naito H, Suehiro JI, Lin Y, Kawaji H, Iba T, Kouno T, Ishikawa-Kato S, Furuno M, Takara K, Muramatsu F, Weizhen J, Kidoya H, Ishihara K, Hayashizaki Y, Nishida K, Yoder MC, Takakura N. CD157 marks tissue-resident endothelial stem cells with homeostatic and regenerative properties. Cell Stem Cell 22:384-397 (2018).

Cutaneous Immunology

Manabu Fujimoto, MD/PhD

Professor	Manabu Fujimoto
Research Assistant	5
Support Staff	2

Our laboratory has made contributions to the understanding of autoimmune skin diseases, with a particular focus on connective tissue disease (especially dermatomyositis and systemic sclerosis), psoriasis, and the roles of B and T cells in immune regulation. Our research combines clinical observation, immunological investigation, and translational medicine to elucidate disease mechanisms and identify therapeutic targets. Recent work has highlighted the importance of immune cell metabolism, the immunoregulatory functions of keratinocytes, and the clinical significance of autoantibody profiles in inflammatory myopathies.

1. Association between periungual changes and myositis-specific autoantibodies in patients with idiopathic inflammatory myopathies: A retrospective cohort study *Journal of the American Academy of Dermatology* (2024)

This retrospective cohort study examined 78 patients with idiopathic inflammatory myopathies and found a strong association between specific periungual changes and the presence of myositis-specific autoantibodies (MSAs). We demonstrated that erythema of the lateral nailfold and hemorrhagic crust or crust of the proximal nailfold were frequently observed in patients with anti-MDA5. Roughening and cracking of the proximal nailfold were more frequently observed in patients with anti-TIF1γ or anti-Mi-2 antibodies. Almost all patients with skin atrophy of the proximal or lateral nailfold had anti-TIF1γ antibodies. These findings suggest that careful dermatological examination can serve as a non-invasive marker for MSA subtypes, offering potential for early diagnosis and risk stratification in dermatomyositis. This study emphasizes the importance of integrating dermatological signs with serological testing to optimize clinical management.

2. Downregulation of Semaphorin 4A in keratinocytes reflects the features of non-lesional psoriasis *eLife* (2024)

In this study, we revealed that Semaphorin 4A (Sema4A), an immunoregulatory molecule, is markedly downregulated in the keratinocytes of both lesional and non-lesional skin in patients with psoriasis. Using transcriptomic analysis and immunostaining, we demonstrated that Sema4A deficiency in keratinocytes leads to epidermal hyperplasia and increased infiltration of IL-17A-producing T cells in an imiquimod-induced psoriasis mouse model. The epidermis of psoriatic non-lesion and Sema4A KO mice demonstrated mTOR complex 1 upregulation, and the application of mTOR inhibitors reversed the skewed expression of cytokeratins in Sema4A KO mice. These findings suggest that Sema4A plays a critical role in maintaining epidermal immune homeostasis and its loss contributes to psoriasis pathogenesis through the mTOR signaling, even in clinically unaffected skin. The results point to a potential therapeutic role for targeting Sema4A-related pathways in early intervention.

3. Augmented Glycolytic Activity in Circulating T Cells of Systemic Sclerosis *Journal of Investigative Dermatology* (2024)

In this translational study, we investigated the metabolic state of peripheral T cells in patients with systemic sclerosis (SSc). They found that CD4+ and CD8+ T cells in SSc exhibit increased glycolytic activity compared to healthy controls. This metabolic shift was associated with elevated expression of glycolysis-

related genes and enhanced production of proinflammatory cytokines. Our in vitro analysis revealed that the inhibition of glycolysis in SSc T cells hampers the production of IFNγ and IL-13 from T cells and collagen production in fibroblasts. The study highlights glycolytic reprogramming as a potential mechanism driving chronic immune activation and tissue fibrosis in SSc. These findings open new avenues for metabolic targeting in autoimmune diseases, particularly in cases where conventional immunosuppression is insufficient.

In addition to our published work, we are actively engaged in several ongoing investigations that further expand the understanding of autoimmune and inflammatory skin diseases. These include the characterization of pathogenic T cells in dermatomyositis and pathogenic B cells in systemic sclerosis, both aimed at defining immune cell subsets that drive tissue-specific pathology. We are also advancing studies on vitiligo, focusing on melanocyte-targeted autoimmunity, and investigating the role of loricrin in coordinating epidermal barrier function, immune responses, and stem cell regulation. Moreover, we are exploring the skin-specific functions of Regnase-1, a key post-transcriptional regulator of inflammation. Together, these studies reflect a comprehensive approach that links epithelial biology with immune regulation, offering new insights into disease mechanisms and identifying promising molecular targets for future therapies.

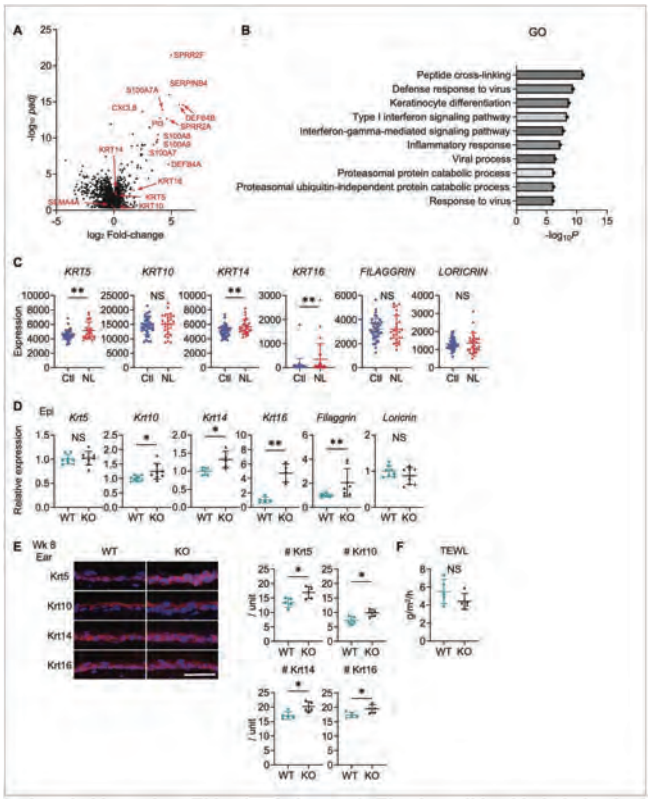


Figure.
Sema4A knockout (KO) skin shares the features of human psoriatic non-lesions (NL).
(A, B) The volcano plot (A) and Gene Ontology (GO) analysis (B), generated from RNA-sequencing data (GSE121212) using RaNAseq, display changes in gene expression in psoriatic NL compared to Ctl. (C) The difference in the expression of epidermal differentiation markers between Ctl and NL (n=38 for Ctl, n=27 for NL) was calculated with the transcripts per million values. **padj<0.01. NS, not significant. The error bars represent the standard deviation. (D) Relative gene expression of epidermal differentiation markers between wk 8 Epi of wild-type (WT) mice and KO mice (n=5 for Krt14 and Krt16, n=8 for Krt5, Krt10, Filaggrin, and Loricrin). (E) Left: Representative immunofluorescence pictures of Krt5, Krt10, Krt14, and Krt16 (red) overlapped with DAPI. Scale bar = 50 μm. Right: Accumulated graphs showing the numbers of Krt5, Krt10, Krt14, and Krt16 positive cells per 100 μm width (n=5 per group) of wk 8 ear (right). Each dot represents the average from 5 unit areas per sample. (F) Transepidermal water loss (TEWL) in back skin of WT mice and KO mice at wk 8 (n=5 per group). (D–F) *p<0.05, **p<0.01. NS, not significant. The error bars represent the standard deviation.

Recent Publications

1. Fujimoto M, Ueda-Hayakawa I. Advancing treatment for idiopathic inflammatory myopathies: insights into immune modulation by JAK inhibition. Rheumatology keaf111 (2025).

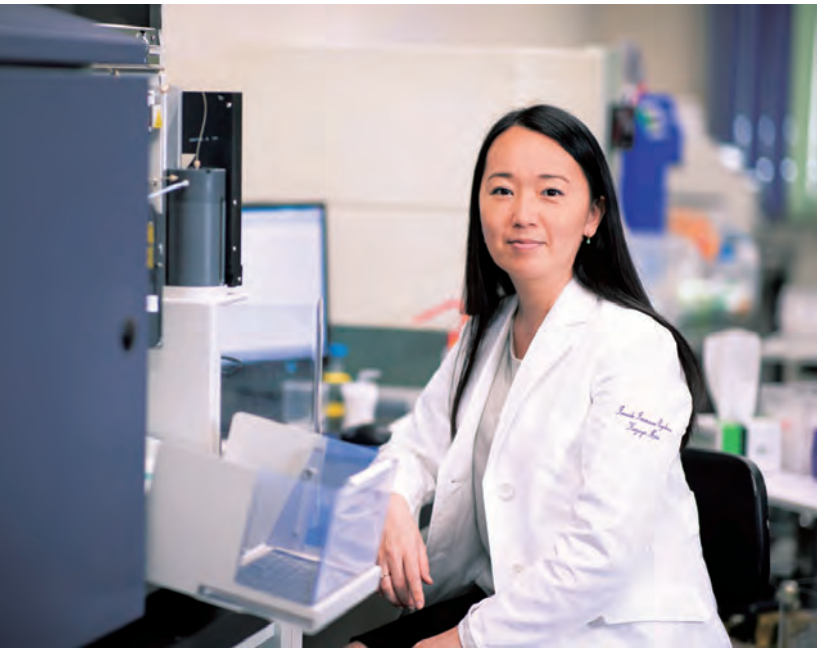
2. Kume M, Koguchi-Yoshioka H, Nakai S, et al. Downregulation of semaphorin 4A in keratinocytes reflects the features of non-lesional psoriasis. Elife. 13:RP97654 (2024).

3. Ueda-Hayakawa I, Maekawa A, Tonomura K, Kaneda E, Yamazaki Y, Arase N, Fujimoto M. Association between periungual changes and myositis-specific autoantibodies in patients with idiopathic inflammatory myopathies: A retrospective cohort study. J Am Acad Dermatol. 91(3):531-533 (2024).

4. Inoue E, Koguchi-Yoshioka H, Kume M, Matsumura Y, Matsuda S, Ueda-Hayakawa I, Watanabe R, Fujimoto M. Augmented Glycolytic Activity in Circulating T Cells of Systemic Sclerosis. J Invest Dermatol. 145(2):432-436.e10 (2025).

5. Connolly CM, Gupta L, Fujimoto M, Machado PM, Paik JJ. Idiopathic inflammatory myopathies: current insights and future frontiers. Lancet Rheumatol. 6(2):e115-e127 (2024).

Innate Immune Systems



Kazuyo Moro, DDS/PhD

Professor	Kazuyo Moro
Associate Professor	Yakuya Yashiro
Assistant Professor	Satoshi Koga
Postdoctoral Fellow	1
Research Assistant	3
Support Staff	2

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia (IIP), characterized by progressive and irreversible fibrosis of the lungs. IPF has a poor prognosis, and no effective treatments are currently available. Therefore, elucidating its underlying pathogenesis and developing new therapeutic strategies remain urgent clinical goals.

To address this, we recently developed and reported a novel mouse model of pulmonary fibrosis driven by endogenous factors (Ifngr1$^{-/-}$Rag2$^{-/-}$ mice; Otaki et al., Nat Commun., 2023). Pulmonary fibrosis is a multifactorial disease caused by both exogenous factors (e.g., smoking, environmental exposures) and endogenous factors such as aging and autoimmune diseases. Most existing studies rely on bleomycin-induced models, which create epithelial injury through drug-induced DNA damage, ultimately leading to transient fibrosis via TGF-β–dependent pathways. However, these models are limited in their ability to mimic fibrosis that arises spontaneously from endogenous factors. In contrast, Ifngr1$^{-/-}$Rag2$^{-/-}$ mice spontaneously develop severe pulmonary fibrosis with age. This strain lacks both IFN-γ and regulatory T cells (Tregs), which normally suppress group 2 innate lymphoid cells (ILC2s). As a result, these mice exhibit enhanced ILC2 activation (Moro et al., Nat Immunol., 2016). We observed that fibrosis in these mice progressed with age and was associated with clinical features such as elevated serum surfactant protein D (SP-D) and significantly reduced peripheral oxygen saturation (SpO_2).

Mechanistically, IL-33–dependent ILC2 activation was found to be essential for fibrosis development. Fibrosis was suppressed in Ifngr1$^{-/-}$Rag2$^{-/-}$ mice lacking ILCs (Ifngr1$^{-/-}$Rag2$^{-/-}$Il2rg$^{-/-}$ mice) or IL-33 (Ifngr1$^{-/-}$Rag2$^{-/-}$IL33$^{-/-}$ mice). Furthermore, depletion of ILC2s using anti-Thy-1 antibodies significantly reduced fibrotic progression. Histological analysis revealed that ILC2s and IL-33–positive fibroblasts accumulated at fibrotic areas, and *in vitro* assays confirmed that ILC2s directly stimulated fibroblasts to produce collagen. We found that fibroblasts began to produce IL-33 themselves, forming a positive feedback loop that perpetuated and exacerbated fibrotic responses.

Our previous studies also showed that crossing RORγ$^{-/-}$ mice (deficient in ILC3s) with Ifngr1$^{-/-}$Rag2$^{-/-}$ mice suppressed fibrosis. However, the mechanisms behind this finding were unclear. In the current study, we investigated the role of ILC3s in regulating fibrosis. We found that ILC3s and neutrophils co-accumulated at fibrotic areas in Ifngr1$^{-/-}$Rag2$^{-/-}$ mice. Given that ILC3s are known to produce neutrophil-attracting chemokines, we hypothesized that they might drive neutrophil recruitment to fibrotic areas. Importantly, we discovered that neutrophils enzymatically cleave full length IL-33 into its mature, highly active form. While fibroblasts initially release IL-33 in its full-length form, proteolytic cleavage by neutrophils enhances its potency for ILC2 activation by approximately 10-fold. In mice lacking ILC3s, IL-33 cleavage was significantly diminished. Moreover, treatment with a RORγt antagonist not only suppressed neutrophil accumulation and IL-33 cleavage but also ameliorated fibrotic symptoms.

These findings indicate that ILC3s serve as a critical initiator of the ILC2–fibroblast feedback circuit by promoting neutrophil-mediated IL-33 activation. Targeting ILC3s may thus offer a novel therapeutic strategy to halt or slow the progression of pulmonary

fibrosis caused by endogenous factors. In conclusion, our Ifngr1$^{-/-}$ Rag2$^{-/-}$ mouse model provides a powerful platform for studying spontaneous pulmonary fibrosis without the need for artificial injury. The identification of the ILC3–neutrophil–IL-33 axis upstream of ILC2 activation highlights new mechanistic insights into disease progression and potential drug targets for fibrotic lung diseases.

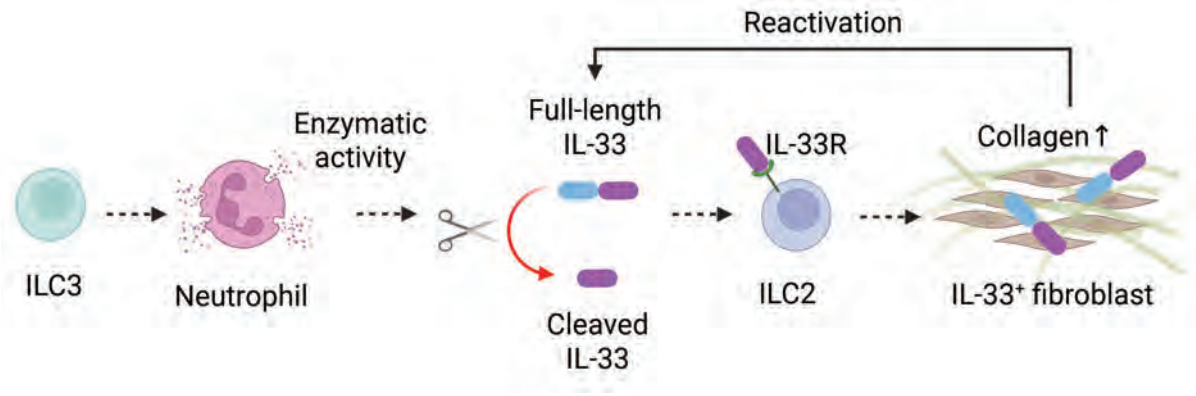


Figure.
Neutrophils recruited by ILC3s accumulate at fibrotic sites and enzymatically cleave full-length IL-33 released from fibroblasts into its active form, which strongly activates ILC2s. Activated ILC2s induce collagen production in fibroblasts and further stimulate IL-33 expression, establishing a self-amplifying positive feedback loop. This loop sustains IL-33 signaling in the fibrotic microenvironment, thereby promoting persistent and progressive fibrosis.

Recent Publications

1. Yamashita M, et al. Cell-type specific, inducible and acute degradation of targeted protein in mice by two degron systems. Nat Commun 15:10129 (2024).
2. Yamagishi M, et al. Quantitative live-cell imaging of secretion activity reveals dynamic immune responses. iScience 27:109840 (2024).
3. Tabata S, et al. NFκB dynamics-dependent epigenetic changes modulate inflammatory gene expression and induce cellular senescence. Febs j 291:4951-4968 (2024).
4. Tanaka Y, et al. Time-dependent cell-state selection identifies transiently expressed genes regulating ILC2 activation. Commun Biol 6:915 (2023).
5. Otaki N, et al. Activation of ILC2s through constitutive IFNγ signaling reduction leads to spontaneous pulmonary fibrosis. Nat Commun 14:8120 (2023).

Human Single Cell Immunology

James Wing, PhD

Professor	James Wing
Assistant Professor	Mara A. Llamas-Covarrubias
Postdoctoral Fellow	1

Our laboratory employs a dual-pronged strategy to advance understanding of human immunology. Our primary approach involves conducting deep immune phenotyping of human cellular responses in patients experiencing infectious diseases and following vaccination. This methodology allows us to precisely identify and track cellular populations undergoing significant changes during these immune challenges. Through detailed phenotypic and functional profiling, we can observe the dynamic shifts in immune cell populations, activation states, and functional capabilities that occur in response to pathogenic threats and prophylactic interventions.

While this approach yields valuable insights into cellular dynamics during immune responses, it inherently presents limitations in elucidating the complex intercellular communication networks that coordinate these responses. To address this gap in our understanding, we have concurrently developed experimental systems designed to measure and quantify cellular interactions with high precision. These platforms enable the direct observation of cell-cell communication events and provide detailed measurements of how immune cells respond to various pharmaceutical interventions, offering a more complete picture of the functional consequences of these interactions.

The integration of these complementary methodologies—deep cellular profiling and interaction-focused experimentation—provides a more holistic understanding of immune system operation than either approach could achieve independently. Our laboratory's recent publications exemplify the value of this dual approach.

- **New Discovery in Antigen-Specific B-Cell Biology:**

Antibody production by antigen-specific B-cells represents a critical component of protective immunity during both infection and vaccination. Through comprehensive multimodal analysis of patient cohorts during COVID-19 infection and following mRNA vaccination, our team has identified and characterized a previously unrecognized B-cell subset. We have designated this novel population as "Activated atypical" B-cells and demonstrated that they constitute the predominant SARS-CoV2-specific B-cell population during both COVID-19 infection and following mRNA vaccination. This significant finding expands our understanding of humoral immune responses and has important implications for vaccine development and immunotherapeutic interventions (Priest et al, Nature Communications, 2024).

- **Innovative Methodology for Regulatory T-Cell Functional Analysis:**

Regulatory T-cells (Tregs) serve as master coordinators of immune responses, playing essential roles in modulating reactions to infectious agents, vaccines, autoimmune triggers, and malignancies. To better understand these critical immunoregulatory cells, our laboratory has developed and implemented novel methodological approaches that enable deeper investigation of Treg functionality. Implementation of these techniques has yielded multiple significant discoveries regarding previously unappreciated aspects of Treg biology (Figure 2). These findings have important implications for understanding immunological homeostasis and developing targeted immunomodulatory therapies for a range of conditions (Søndergaard et al, Nature Communications, 2025).

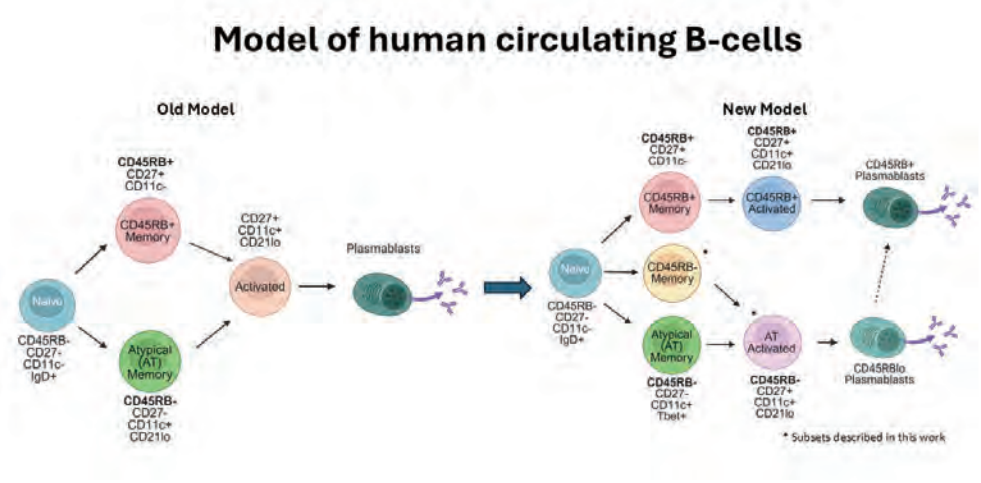


Figure 1.

New model of circulating memory B-cells.

We found that human activated memory B-cells could be split into two sub lineages based on differential expressions of the marker CD45RB. This allows a new model of B-cells that more clearly separate which cells are responding to vaccination and infection.

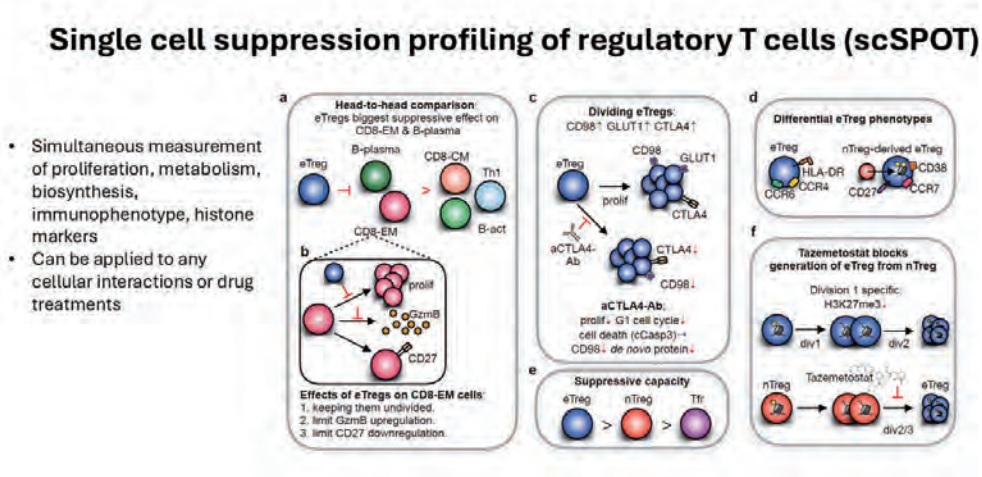


Figure 2.

Key findings of Søndergaard, et al. Nature Communications, 2025

(**a**) We found that Effector Tregs (eTregs) most strongly affect effector memory CD8 (CD8-EM) cells and B-plasma cells. (**b**) eTregs control CD8-EM cells by stopping their division and reducing the cytotoxic molecule Granzyme B while maintaining CD27. (**c**) eTregs division is blocked by anti-CTLA4 antibodies (**d**) A specific group of $CD38^{+}HLADR^{-}$ effector Tregs is a biomarker of Critical COVID-19 (Søndergaard et al, PNAS, 2023). Using this technique, we were able to demonstrate that these cells have recently been converted from naïve Tregs. Together these findings suggest that conversion of naïve Tregs to the specific group of $CD38^{+}HLADR^{-}$ effector is an indicator of the severity of COVID-19 infection. (**e**) Ranks different Treg types by their suppressive ability, with eTregs being strongest. (**f**) Demonstrates how the epigenetic inhibitor drug Tazemetostat blocks naive Tregs from becoming eTregs during early cell division.

Recent Publications

1. Søndergaard J, Tulyeu J, Priest D, Sakaguchi S, Wing JB. Single cell suppression profiling of human regulatory T cells. Nat Commun. 16(1):1325 (2025).
2. Sakakibara S, et al. Clonal landscape of autoantibody-secreting plasmablasts in COVID-19 patients. Life Sci Alliance. 7(12):e202402774 (2024).
3. Ahmed A, et al. CTLA-4-expressing ILC3s restrain interleukin-23-mediated inflammation. Nature 630(8018):976-983 (2024).
4. Priest D, et al. Non-classical CD45RBlo memory B-cells are the majority of circulating antigen-specific B-cells following mRNA vaccination and COVID-19 infection. Nat Commun. 15(1):6811 (2024).
5. Søndergaard JN, et al. A sex-biased imbalance between Tfr, Tph and atypical B cells, determines antibody responses in COVID-19 patients. Proc Natl Acad Sci USA. 120(4):e2217902120 (2023).

Human Immunology (Single Cell Genomics)

Daisuke Okuzaki, PhD

Associate Professor	Daisuke Okuzaki
Assistant Professor	Yuchen Liu
Postdoctoral Fellow	2
Visiting Scientist	2
Support Staff	1

Since its establishment in November 2019, the Laboratory of Human Immunology has developed a single-cell analysis platform at IFReC and now serves as the NGS core facility. Over the years, it has evolved into Japan's leading center for single-cell analysis, advancing the application of single-cell sequencing to connect fundamental research with clinical practice.

During the COVID-19 pandemic, our lab played a pivotal role in single-cell RNA analysis as part of Team Handai, a university-wide COVID-19 research group, analyzing over 200 peripheral blood mononuclear cell (PBMC) samples and contributing to major discoveries published in Nature and Nature Genetics. Our participation in the Coronavirus Task Force deepened our understanding of COVID-19 mechanisms. In parallel, our proteomics research using Olink's Explore 1536 identified key blood proteins associated with COVID-19 severity, providing superior diagnostic and prognostic markers.

A significant discovery during this period was the novel public antibody clonotype PA-N-CoV1804, which reacts with both SARS-CoV-2 N protein and self-antigens. It underwent robust clonal expansion in a subset of COVID-19 patients and was exclusively expressed in plasmablasts. Our findings showed PA-N-CoV1804 originated from naive B cells and expanded de novo following SARS-CoV-2 infection. This study was published in Life Science Alliance in December 2024, offering key insights into antibody responses in COVID-19 patients.

As the pandemic subsided, our research shifted to vaccine-induced immune responses. We conducted scRNA-seq analysis on a patient with encephalitis following COVID-19 vaccination, identifying a distinct myeloid cell subset present only during the acute phase. This suggested a potential link between vaccination and transient immune dysregulation. Further cerebrospinal fluid (CSF) analysis was warranted to clarify its pathogenic role. These findings were published in *Frontiers in Immunology* on February 23, 2023.

Building on this, we investigated endogenous circRNAs in response to BNT162b2 mRNA vaccination. CircRNAs, characterized by their covalently closed structures, exhibit high pharmaceutical stability. They have been linked to various diseases, serving as potential biomarkers and therapeutic targets. We performed full-length nanopore sequencing on peripheral blood samples from five healthcare workers before vaccination, after the first dose, and after the second dose of BNT162b2. We detected 4706 circRNAs, with 4217 novel circRNAs specifically expressed during vaccination. These circRNAs were enriched in stress granule assembly and SARS-CoV-2 RNA binding protein motifs, including PABPC1, PUM1, and YBX1. Additionally, 489 circRNAs were as previously reported miRNA sponges. The differentially expressed circRNAs primarily originated from plasma B cells, distinguishing them from known blood circRNAs. This study, revealing dynamic circRNA expression changes post-vaccination, was published in Gene in September 2024 (Figure).

To further this research, we collected 48 additional PBMC samples, including those from cohorts sampled 200 days after the second vaccination, to deepen our understanding of long-term circRNA responses to mRNA vaccination.

Beyond COVID-19, our lab has advanced both single-cell and long-read sequencing technologies. We applied direct RNA sequencing to study Vibrio parahaemolyticus, uncovering a more complex bacterial transcriptome than previously recognized. Additionally, we developed methodologies for simultaneous bacterial and eukaryotic cell detection at the single-cell level and enhanced circRNA detection using long-read sequencing.

International Collaborations

Through collaboration with a nanotechnology research team in Taiwan, we explored the application of nanoparticle-based immunotherapy. This partnership led to multiple high-impact publications, highlighting the successful integration of nanotechnology and immunology and demonstrating novel strategies to enhance cancer immunotherapy through nanoparticle-mediated antigen presentation and immune activation.

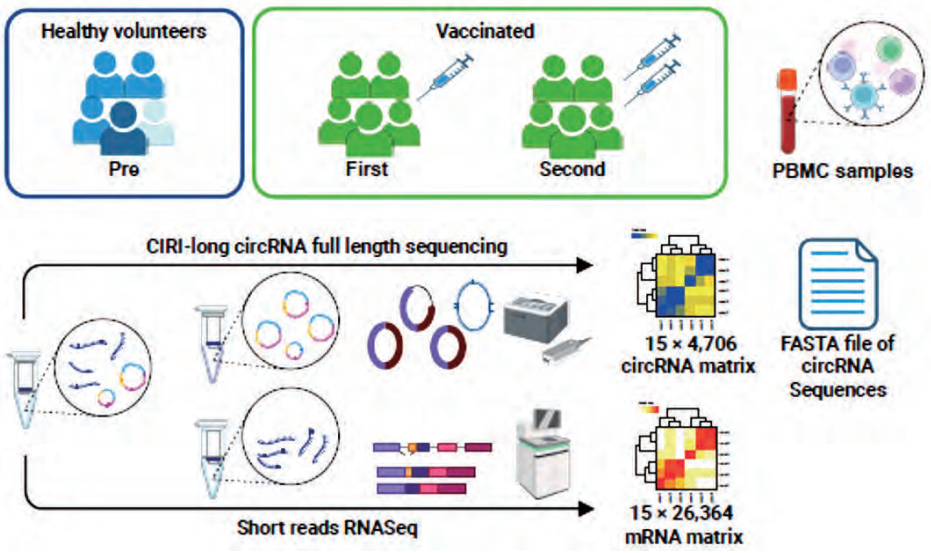


Figure.
Endogenous circRNAs in response to BNT162b2 mRNA vaccination.

Recent Publications

1. Al Kadi M, Yamashita M, Shimojima M, Yoshikawa T, Ebihara H, Okuzaki D, Kurosu T. Cytokine storm and vascular leakage in severe dengue: insights from single-cell RNA profiling. Life Sci Alliance. 8(6):e202403008 (2025).

2. Liu YC, Ishikawa M, Sakakibara S, Kadi MA, Motooka D, Naito Y, Ito S, Imamura Y, Matsumoto H, Sugihara F, Hirata H, Ogura H, Okuzaki D. Full-length nanopore sequencing of circular RNA landscape in peripheral blood cells following sequential BNT162b2 mRNA vaccination. Gene. 933:148971 (2025).

3. Sakakibara S, Liu YC, Ishikawa M, Edahiro R, et al. Clonal landscape of autoantibody-secreting plasmablasts in COVID-19 patients. Life Sci Alliance. 7(12):e202402774 (2024).

4. Kurosu T, Okuzaki D, Sakai Y, Kadi MA, Phanthanawiboon S, Ami Y, Shimojima M, Yoshikawa T, Fukushi S, Nagata N, Suzuki T, Kamimura D, Murakami M, Ebihara H, Saijo M. Dengue virus infection induces selective expansion of Vγ4 and Vγ6TCR γδ T cells in the small intestine and a cytokine storm driving vascular leakage in mice. PLoS Negl Trop Dis. Nov 8;17(11):e0011743 (2023).

5. Ishikawa M, Shimada Y, Ozono T, Matsumoto H, Ogura H, Kihara K, Mochizuki H, Okuno T, Sakakibara S, Kinoshita M, Okuzaki D. Single-cell RNA-seq analysis identifies distinct myeloid cells in a case with encephalitis temporally associated with COVID-19 vaccination. Front Immunol. 14:998233 (2023).

Immune Homeostasis

Yasutaka Okabe, PhD

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Postdoctoral Fellow	1
Research Assistant	2
Support Staff	1

Immune system in the body cavity

Intra-abdominal infection is the second most common cause of life-threatening sepsis and requires prompt medical intervention. Infections within the abdominal (peritoneal) cavity can arise from pathological or traumatic disruption of the intestinal wall, cirrhosis, pancreatitis, abdominal surgery, or peritoneal dialysis.

Peritoneal macrophages play a critical role in abdominal immunity. We discovered that the transcription factor GATA6, which is selectively expressed in macrophages within the peritoneal cavity, functions as a master transcriptional regulator driving the functional specialization of peritoneal macrophages (Cell, 2014). Deletion of the *Gata6* gene in these cells disrupted the peritoneal-specific gene expression program, leading to impaired macrophage positioning, diminished local proliferation, and compromised immune responses unique to the peritoneal environment. We further identified retinoic acid, a lipophilic metabolite derived from vitamin A, as a key regulator of *Gata6* expression. Consistently, vitamin A deficiency in mice significantly reduced *Gata6* expression, confirming the critical role of retinoic acid signaling in this regulatory pathway.

In addition to macrophages, the milky spots of the omentum are non-classical lymphoid structures that play an essential role in orchestrating immune responses in the peritoneal cavity. These structures act as hubs for antigen and particle capture, lymphocyte recruitment, immune cell differentiation, and local germinal center formation. Milky spots possess hybrid characteristics of both secondary and tertiary lymphoid tissues. While their development is programmed during fetal life, they can also form postnatally in response to peritoneal stimuli such as inflammation, infection, obesity, or tumor metastasis. However, the mechanisms governing their formation remain poorly understood. We identified a specialized subset of fibroblastic reticular cells (FRCs) in the omentum that express enzymes responsible for converting vitamin A to retinoic acid (J. Exp. Med, 2023). These FRCs are uniquely present in milky spots but absent from conventional lymph nodes. We found that they are essential for the recruitment of circulating lymphocytes into the milky spots, a process driven by retinoic acid–dependent induction of the chemokine CXCL12. Taken together, our findings reveal a stromal–immune cell interaction network that underlies the formation of non-classical lymphoid tissues in the peritoneal cavity. Our study highlights the central roles of GATA6, retinoic acid, and FRCs in regulating peritoneal immune responses and provides new insights into tissue-specific immunity.

Respiratory defense mechanism

The respiratory system employs multiple defense mechanisms to prevent infections, including phagocytic activity by alveolar macrophages and mucociliary clearance (MCC) in the airways (Figure). Our goal is to elucidate the fundamental mechanisms underlying these protective systems and to develop preventive and therapeutic strategies for a wide range of respiratory infections. Among these defenses, the airway serves as the first line of protection, acting not only as a physical barrier but also playing an active role in removing inhaled pathogens and particulates via MCC. This clearance system relies on two key components: mucus, secreted by goblet cells and submucosal glands, which traps pathogens and particles; and the coordinated, rhythmic beating of cilia on ciliated epithelial cells, which propels the mucus toward the pharynx for elimination through swallowing. We have identified aldehyde metabolism as a critical

factor in maintaining mucociliary clearance, highlighting its importance in sustaining airway defense and homeostasis.

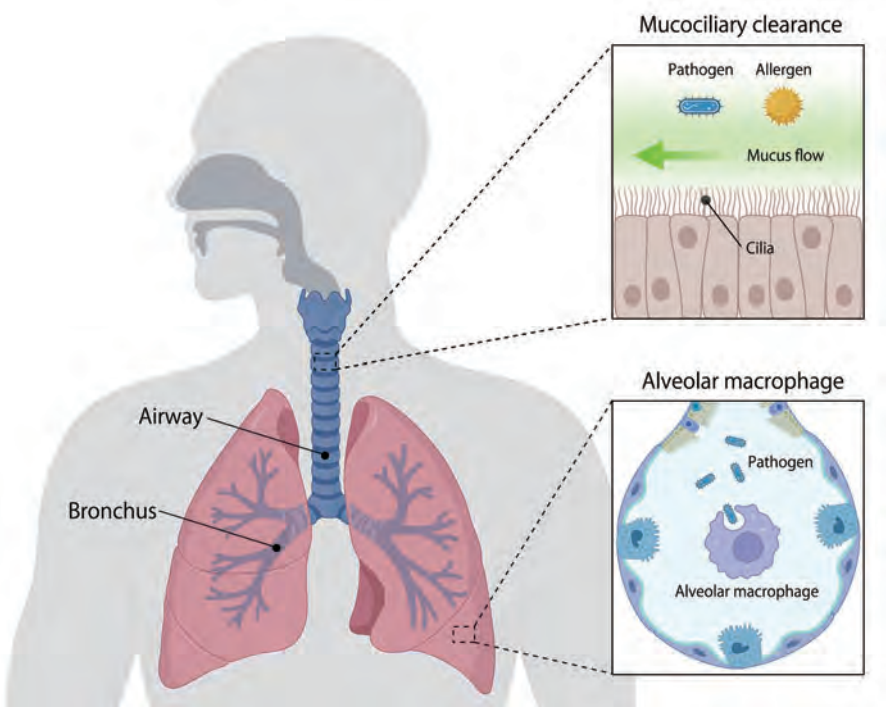

Figure.
The respiratory system is equipped with unique infection defense mechanisms, such as mucociliary clearance in the airways and phagocytic activity by alveolar macrophages.

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1. Nakayama Y, Sasai M, Kuratani A, Okamoto M, Okuzaki D, Yamamoto K, Ono C, Yamaguchi M, Kawabata S, Shinjyo N, Okabe Y, Matsuura Y, Ato M, Yamamoto M. Targeted labeling and depletion of alveolar macrophages using VeDTR mouse technology. iScience 28(3):111975 (2025). doi: 10.1016/j.isci.2025.111975.

2. Okabe Y. Development and organization of omental milky spots. Immunol Rev. 324(1):68-77 (2024). doi: 10.1111/imr.13337.

3. Luca D, Lee S, Hirota K, Okabe Y, et al. Aberrant RNA sensing in regulatory T cells causes systemic autoimmunity. Sci Adv. 10(9):eadk0820 (2024). doi: 10.1126/sciadv.adk0820.

4. Yoshihara T. & Okabe Y. Aldh1a2+ fibroblastic reticular cells regulate lymphocyte recruitment in omental milky spots. J Exp Med. 220(5) e20221813 (2023).

Cellular Immunotherapy

Naoki Hosen, MD/PhD

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Our focus is on cellular immunotherapy, in particular chimeric antigen receptor (CAR) T-cell therapy for cancer. CAR T cells targeting CD19 or BCMA show surprisingly high efficacy against B-cell leukemia/lymphoma or multiple myeloma. We discovered that the active conformer of an integrin may serve as a specific therapeutic target for multiple myeloma (MM), an incurable hematologic cancer characterized by the accumulation of neoplastic plasma cells in the bone marrow (BM). The clinical trial of the CAR T-cell targeting the active conformation of integrin b7 for MM is ongoing. We have also identified R8H283 as a mAb that binds to MM cells but not to normal hematopoietic or non-hematopoietic cells. R8H283 specifically recognized CD98hc. Although CD98 heterodimers were also expressed on normal leukocytes, R8H283 did not react with them. Normal leukocytes expressed CD98hc glycoforms different from those expressed by MM cells, which may account for the lack of R8H283 reactivity in normal leukocytes. R8H28-derived CAR T cells exerted significant anti-tumor effects without harming normal hematopoietic cells. These findings suggest that a cancer-specific conformational epitope in a ubiquitous protein, which cannot be identified by transcriptome or proteome analysis, can be found by extensive screening of primary human tumor samples.

Identification of a novel target antigen for acute myeloid leukemia relapsed after allogeneic hematopoietic cell transplantation and development of CAR-T and CAR NK cells targeting it

Acute myeloid leukemia (AML)-specific target antigens are difficult to identify. Among 14,000 monoclonal antibodies (mAbs) raised against AML cells, we identified KG2032 as an mAb that bound specifically to AML cells in about half of patients, but not to normal leukocytes other than B lymphocytes. KG2032 reacted with a subset of HLA-DRB1 molecules, specifically those in which the 86th amino acid was not aspartic acid. KG2032 reacted minimally with non-hematopoietic tissues. These results indicate that KG2032 reactivity is highly specific for AML cells in patients carrying KG2032-reactive HLA-DRB1 alleles who received allo-HCT from a donor carrying KG2032-non-reactive HLA-DRB1 alleles. KG2032-derived CAR T or NK cells exerted a significant anti-leukemic effect, suggesting that they have the potential to cure many AML patients who are currently incurable even with allo-HCT.

We have also applied the same strategy to various types of solid tumors in collaboration with various cancer treatment departments at Osaka University Hospital. We recently demonstrated that our screening method also works in glioblastoma. In addition, we are now focusing on the development of cord blood-derived cell therapy, including CAR NK cell therapy.

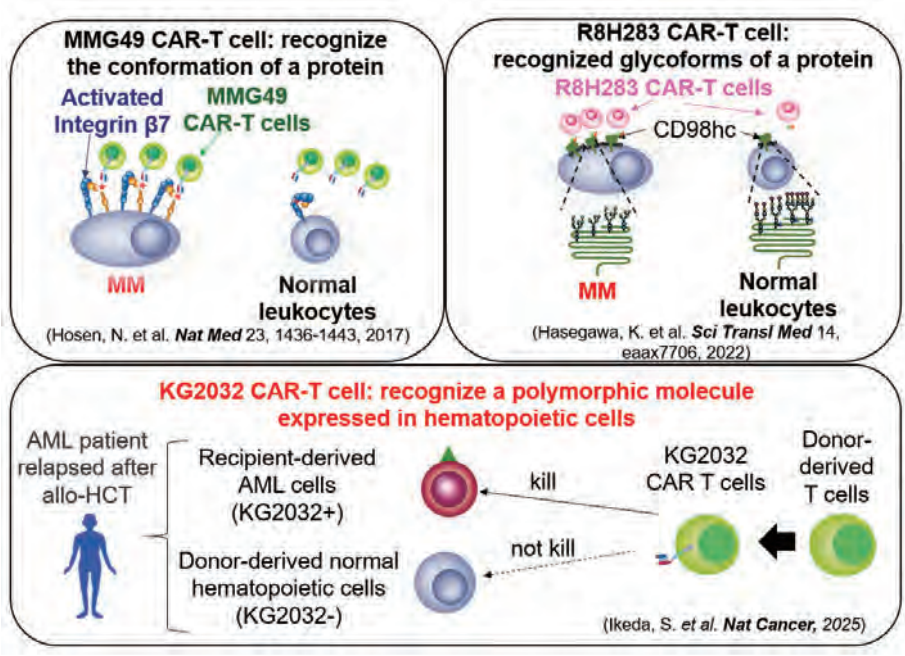

Figure 1.
New types of target antigens of CAR T cells.

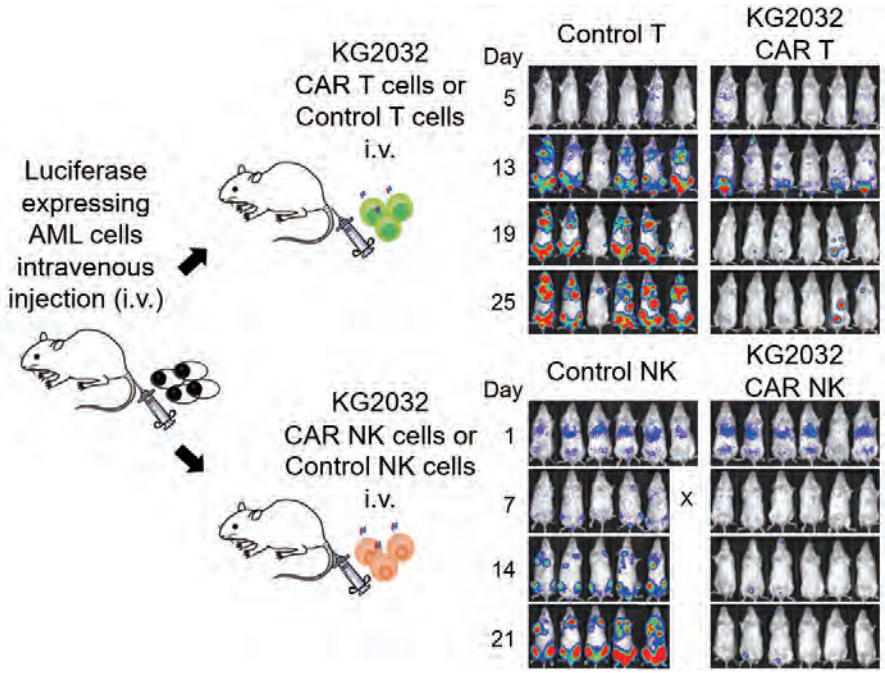

Figure 2.
Anti-leukemia effect of KG2032 CAR T or CAR NK cells in mouse xenograft models.

Recent Publications

1. Ikeda S. et al. CAR T or NK cells targeting mismatched HLA-DR molecules in acute myeloid leukemia after allogeneic hematopoietic stem cell transplant. Nat Cancer. (2025). doi: org:10.1038/s43018-025-00934-1

2. Yaga M. et al. CD98 heavy chain protein is overexpressed in non-small cell lung cancer and is a potential target for CAR T-cell therapy. Sci Rep. 14:17917 (2024).

3. Wibowo T. et al. CAR-NK cells derived from cord blood originate mainly from CD56(-)CD7(+)CD34(-)HLA-DR(-)Lin(-) NK progenitor cells. Mol Ther Methods Clin Dev. 32:101374 (2024).

4. Hasegawa K. et al. Selective targeting of multiple myeloma cells with a monoclonal antibody recognizing the ubiquitous protein CD98 heavy chain. Sci Transl Med.14:eaax7706 (2022).

5. Hosen N. et al. The activated conformation of integrin beta7 is a novel multiple myeloma-specific target for CAR T cell therapy. Nat Med. 23:1436-1443 (2017).

Microbiology and Immunology

Nobuhiko Kamada, PhD

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	Hiroko Kitamoto
Assistant Professor	Kohei Sugihara
Postdoctoral Fellow	1
Research Assistant	2
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Our team has been studying the role of microbiota in the pathogenesis of gastrointestinal diseases, such as inflammatory bowel disease (IBD) and colorectal cancer (CRC). It has been reported that certain pathogenic members of commensal bacteria (namely 'pathobionts') are enriched under disease conditions and contribute to disease pathogenesis. However, the precise mechanisms by which such pathobionts thrive in disease conditions and trigger and/or exacerbate disease remain incompletely understood.

Adherent–invasive *Escherichia coli* (AIEC) is a pathobiont associated with inflammatory bowel disease (IBD). Our research focuses on understanding the mechanisms by which AIEC adapts to the gut environment and promotes inflammation. Specifically, we investigate the unique metabolic pathways that AIEC exploits during gut colonization and seek to identify "metabolic supporters" that facilitate its persistence. In this context, we have shown that mucolytic bacteria, such as *Akkermansia muciniphila*, degrade the protective mucus layer, thereby enabling AIEC to access and colonize the epithelial niche. Within this niche, AIEC reprograms its metabolism to utilize niche-specific nutrients, such as amino acids pooled in epithelial cells. Beyond AIEC and its role in IBD, we are also identifying other pathobionts associated with a range of gastrointestinal diseases, including colorectal cancer (CRC) and intestinal fibrosis. Our goal is to elucidate the mechanisms by which these microbes adapt to disease-specific environments. Additionally, our research explores the microbial and immune connections between the oral and gut mucosae in the pathogenesis of gastrointestinal diseases. We are investigating the roles of microbial and immune axes that link oral inflammation to gut inflammation. For example, we study immune cells generated during oral inflammation that translocate to the gut mucosa, as well as oral pathobionts capable of migrating to the gut and contributing to disease in ectopic sites. Moreover, we are examining the role of early-colonizing bacteria in maintaining host health during infancy and later in adulthood. In particular, we focus on the impact of maternal bacterial transmission on infant health and susceptibility to disease.

Note: The PI is jointly appointed at IFReC and the University of Michigan (USA). These research projects were conducted at either IFReC or the University of Michigan.

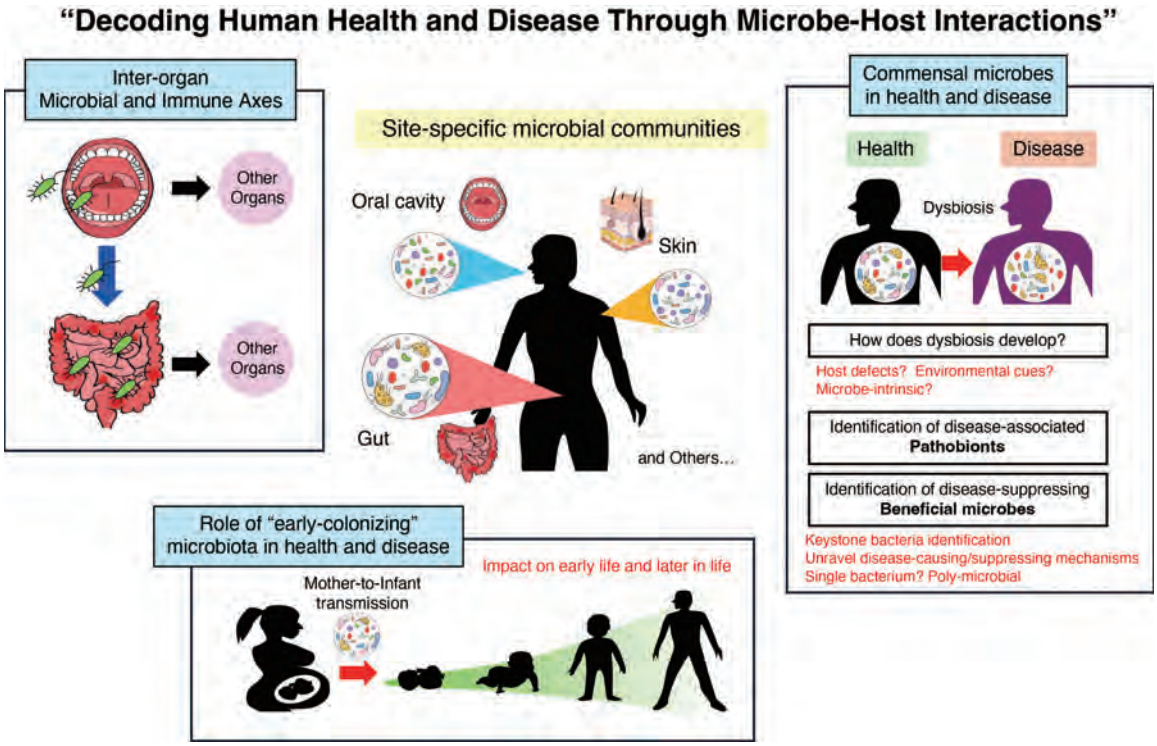

Figure.
Our goal is to unravel the complexities of human health and disease by investigating host–microbe interactions.

Recent Publications

1. Guo Y, Kitamoto S, Caballero-Flores G, Kim Y, Watanabe D, Sugihara K, Núñez G, Alteri CJ, Inohara N, Kamada N. Oral pathobiont Klebsiella chaperon usher pili provide site-specific adaptation for the inflamed gut mucosa. Gut Microbes. 16(1):2333463 (2024).

2. Sugihara K, Kitamoto S, Saraithong P, Nagao-Kitamoto H, Hppstal M, McCarthy C, Rosevelt A, Muraleedharan CK, Gillilland III MG, Imai J, Omi M, Bishu S, Kao JY, Alteri CJ, Barnich N, Schmidt TM, Nusrat A, Inohara N, Golob JL, Kamada N. Mucolytic bacteria license pathobionts to acquire host-derived nutrients during dietary nutrient restriction. Cell Reports. 40(3):111093 (2022).

3. Kitamoto S, Nagao-Kitamoto H, et al. The intermucosal connection between the mouth and gut in commensal pathobiont-driven colitis. Cell 182(2):447-462 (2020).

4. Nagao-Kitamoto H, Leslie JL, Kitamoto S, et al. Interleukin-22-mediated host glycosylation prevents Clostridioides difficile infection by modulating the metabolic activity of the gut microbiota. Nat Med. 26(4):608-617 (2020).

5. Kitamoto S, Alteri CJ, Rodrigues M, Nagao-Kitamoto H, et al. Dietary L-serine confers a competitive fitness advantage to Enterobacteriaceae in the inflamed gut. Nat Microbiol. 5(1):116-125 (2020).

Cutaneous Allergy and Host Defense

Yumi Matsuoka-Nakamura, MD/PhD

Professor	Yumi Matsuoka-Nakamura
Assistant Professor	Shuo Li
Postdoctoral Fellow	2
Support Staff	6

Our laboratory, founded in November 2022, is dedicated to elucidating the molecular, immunological, and ecological mechanisms that govern host–microbe interactions in inflammatory skin diseases, with a primary focus on atopic dermatitis (AD). Our research encompasses two major axes: (1) the role of the skin barrier and its interaction with resident microbial communities and (2) the evolutionary dynamics of methicillin-resistant *Staphylococcus aureus* (MRSA) under selective pressure in hospital settings.

A core area of investigation centers on the accessory gene regulator (Agr) quorum sensing (QS) system in *S. aureus* and its role in bacterial virulence, immune evasion, and long-term colonization. Quorum sensing is a cell-density–dependent communication system that enables bacteria to coordinate gene expression across populations. Our work has shown that Agr is a critical modulator of bacterial behavior, influencing not only toxin production and adhesion but also interactions with the host immune system. The functional state of Agr—whether intact or disrupted—may thus serve as a determinant of microbial pathogenicity and persistence in both community and clinical environments.

In a previously published longitudinal cohort study involving Japanese infants, we demonstrated that early colonization of facial skin by *S. aureus* significantly increased the risk of developing AD by one year of age. Importantly, we identified that spontaneous mutations leading to Agr dysfunction were more frequently observed in isolates from infants who remained healthy. These results suggest that impaired QS function may attenuate virulence and favor a more balanced, less inflammatory host–microbe relationship in early life.

Building on these findings, in 2024 we extended our investigation into the influence of early-life skincare practices and the skin microbiome on the development of allergic diseases. We analyzed a prospective birth cohort of 177 infants who received topical moisturizer-based skincare interventions from the neonatal period. By 12 months of age, 13 infants (7.3%) had developed AD and 3 infants (1.7%) were diagnosed with food allergy (FA), with one overlapping case. Furthermore, a substantial proportion of the cohort (34.5%) exhibited egg white sensitization without clinical symptoms.

Our microbial profiling revealed that dysbiosis—characterized by an increased abundance of *Streptococcus* species and reduced *Cutibacterium acnes*—was evident in neonatal skin samples of infants who later developed AD. Notably, this dysbiotic pattern was mitigated in infants who consistently used moisturizers. Regular application of topical moisturizers correlated negatively with *Streptococcus* levels and positively with *C. acnes*, suggesting that skincare practices in early infancy may actively modulate the developing skin microbiota. These changes may, in turn, influence immune system maturation, reduce aberrant inflammatory signaling, and ultimately lower the risk of allergic disease development. This work underscores the potential for non-pharmaceutical, low-risk interventions to reshape the early-life cutaneous environment and improve health outcomes.

In parallel, we initiated a new project focused on MRSA adaptation in hospital environments, using isolates from an outbreak in a neonatal intensive care unit in Japan. This investigation seeks to clarify how clinical strains of *S. aureus* evolve under antimicrobial and immunological pressures. We are conducting whole-genome sequencing, methylome profiling, and functional assays to determine how factors such as Agr activity, DNA methylation signatures, and stress-response

regulators contribute to bacterial survival, immune evasion, and persistence in the hospital setting. Our early data suggest that epigenetic modulation and QS attenuation may synergize to produce "stealth phenotypes" capable of avoiding host defenses while maintaining colonization.

Looking ahead, we aim to expand our research to better understand how early-life skin environments influence long-term immune phenotypes and disease trajectories. By integrating multi-omics data from human birth cohorts with mechanistic insights from gnotobiotic and genetic mouse models, we plan to identify microbial and host features that predict or prevent disease susceptibility. Particular emphasis will be placed on defining the microbial and immunological signatures that distinguish infants who maintain skin health and immune tolerance—despite environmental challenges—from those who develop chronic inflammatory disorders.

In the broader context of dermatology and infectious disease research, our laboratory seeks to bridge fundamental mechanistic studies with clinical and translational applications. Our findings have implications for the development of novel biomarkers, therapeutic targets, and predictive tools for risk stratification. The potential to manipulate microbial community dynamics or leverage specific immune-modulatory microbes represents a promising frontier in precision medicine. Furthermore, our work on MRSA evolution may inform hospital infection control strategies and guide the design of next-generation antimicrobial agents or prophylactic interventions.

Through these efforts, we are committed to contributing foundational knowledge to the field of skin microbiology and immunology, with the goal of improving disease prevention, diagnosis, and care for vulnerable populations—particularly in early life.

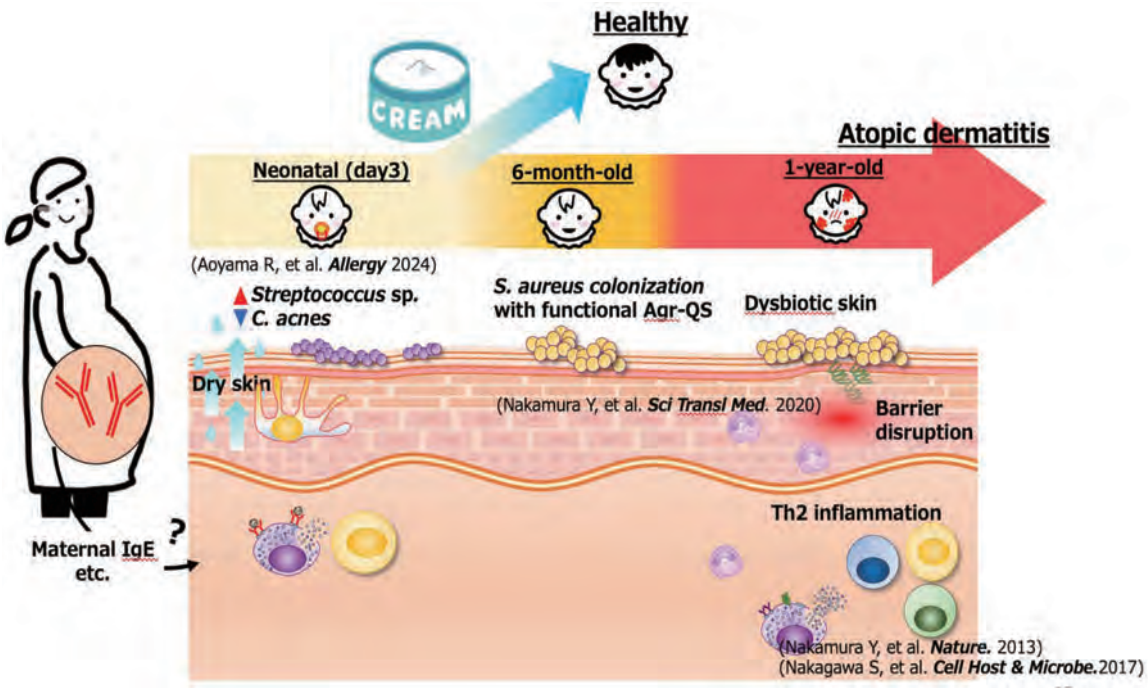

Figure.
Early-life skin microbiota dynamics to the development of atopic dermatitis.

Recent Publications

1. Yamazaki Y, Ito T, Nakagawa S, et al. Altered genomic methylation promotes Staphylococcus aureus persistence in hospital environment. Nat Commun. 15(1):9619 (2024).
2. Aoyama R, Nakagawa S, Ichikawa Y, et al. Neonatal skin dysbiosis to infantile atopic dermatitis: Mitigating effects of skin care. Allergy. 2024; doi: 10.1111/all.16095.
3. Yamazaki Y, Ito T, Tamai M, Nakagawa S, Nakamura Y. The role of Staphylococcus aureus quorum sensing in cutaneous and systemic infections. Inflamm Regen. 44(1) (2024).
4. Matsumoto M, Nakagawa S, Zhang L, Nakamura Y, Villaruz AE, Otto M, Wolz C, Inohara N, Núñez G. Interaction between Staphylococcus Agr virulence and neutrophils regulates pathogen expansion in the skin. Cell Host Microbe. 29(6):930-940 (2021).
5. Nakamura Y, Takahashi H, Takaya A, et al. Staphylococcus Agr virulence is critical for epidermal colonization and associates with atopic dermatitis development. Sci Transl Med. 12(551): eaay4068 (2020).

Single Molecule Imaging

Toshio Yanagida, PhD
Ben Seymour, MD/PhD

Professor	Toshio Yanagida
	Ben Seymour

Tissue injuries are common across animal species, resulting from predator-prey interactions, intraspecific conflicts, accidental trauma, and other natural threats. In ecological settings, animals from various evolutionary lineages (e.g., mammals, cephalopods) exhibit a consistent pattern of behaviours following injury. These behaviours likely reflect evolutionarily optimized responses to the altered homeostatic state associated with physical vulnerability and recovery. Typical responses include heightened pain sensitivity, reduced movement and exploration, increased vigilance, and greater sensitivity to threats. These behaviours closely resemble human symptoms commonly reported after injury, such as persistent (tonic) pain, fatigue, and altered mood or anxiety levels.

This pattern suggests the presence of a central, injury-specific mechanism that adaptively modulates pain and motivational circuits to promote self-protection and prioritize recovery and healing (Seymour, 2023). Although the exact nature of this mechanism is not yet fully understood, it may offer valuable insights into high-level behavioural regulation (i.e., behavioural allostasis). It could also shed light on why multiple psychological symptoms frequently co-occur in clinical (maladaptive) chronic pain, potentially identifying novel treatment targets.

Our core hypothesis is that there exists a coordinated process that detects and tracks injury, adaptively regulating behaviour throughout the healing period. This system likely generates an internal representation of the injury, orchestrates behavioural responses—including the experience of tonic pain—and interacts with other physiological and motivational processes, adjusting acute (phasic) pain responses in accordance with the organism's overall needs.

We have been testing key predictions of this theory. First, we have shown how tonic pain – the core sensory injury signal – controls behaviour. We've developed an experimental paradigm using virtual reality based on foraging for fruit and avoiding harm, to closely mimic ecologically valid tasks. We've shown how tonic pain selectively and specifically modulates motivational vigour, in keeping with a recuperative control process (Tong et al, 2025). Second, we've show how tonic pain also re-values stored memories of previous harm (associative pain memories), in keeping with tonic pain being represented as a homeostatic state (akin to hunger or thirst) (Hewitt et al, 2025). Third, we've shown in a clinical context (inflammatory arthritis) how reward and punishment sensitivity are modulated in accordance with computational models (Mancini et al, 2024). Finally, we have refined an overarching computational description that captures this putative injury behaviour as a core homeostatic system. This then leads to further testable predictions about exactly how I jury information is represented in the brain, and the decision-processes that governs things like pain modulation – as these are key targets for therapeutics.

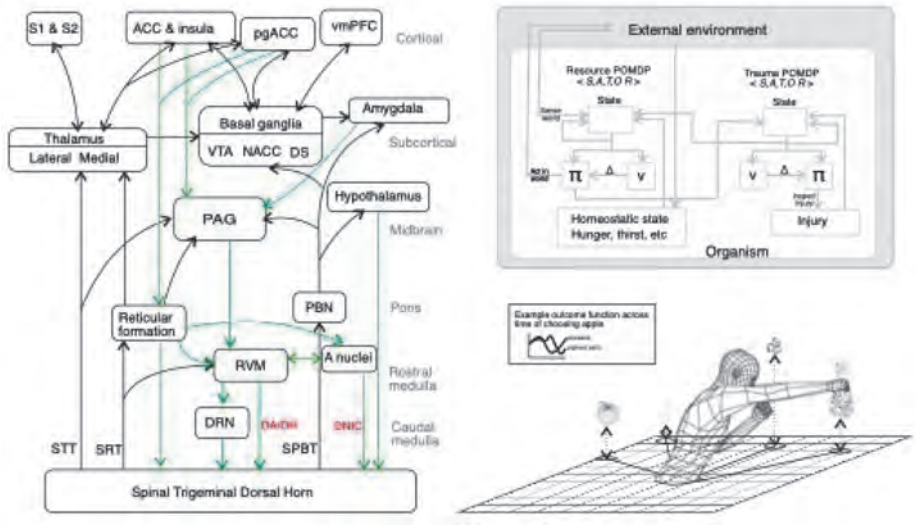

Figure.

The injury system.

The left panel shows key brain nuclei proposed to govern behaviour following injury, outlining a network of brainstem and subcortical sites with recurrent connections to higher cortical sites. Together, these sense information related to the nature and severity of injury, maintain core central representations of it, and modulate efferent behaviour accordingly. The right upper panel provides a computational summary of information processing, expressed as a control system mediating multiple, sometimes competing homeostatic priorities. The right lower panel illustrates the sorts of experiments we do to disentangle behaviour, illustrating a wireframe schematic of a virtual reality based task in which value-based and motor control decision-making can be measured and modelled.

Recent Publications

1. Mahajan P, Dayan P, and Seymour B. Homeostasis After Injury: How Intertwined Inference and Control Underpin Post-Injury Pain and Behaviour. bioRxiv. pp.2025-02.

2. Tong S, Denison T, Hewitt D, Lee SW. and Seymour B. Phasic and tonic pain serve distinct functions during adaptive behaviour. bioRxiv. pp.2025-02.

3. Hewitt D, Tong S, Schreiber S. and Seymour B. Tonic pain revalues associative memories of phasic pain. bioRxiv. pp.2025-03.

4. Mancini F, et al. Enhanced behavioural and neural sensitivity to punishments in chronic pain and fatigue. Brain (2024).

5. Seymour B, Crook RJ, Chen ZS. Post-injury pain and behaviour: a control theory perspective. Nature Rev Neurosci. 1-15 (2023).

Immunology and Cell Biology

Masaru Ishii, MD/PhD

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	Kentaro Fujii
Postdoctoral Fellow	3
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Support Staff	2

During *in vivo* imaging, when a strong laser is irradiated locally (laser ablation), the cells in that area undergo necrosis, releasing damage-associated molecules (DAMPs), which attract inflammatory cells such as neutrophils. This method has been reported as a quantitative approach for evaluating local tissue inflammatory responses in skin and other tissues. In this study, we established a liver imaging system to investigate the molecular mechanisms regulating inflammatory responses in the liver, performed laser ablation, and observed inflammatory responses. As a result, we indeed observed neutrophil accumulation following laser ablation; however, the results varied significantly between experiments, with some showing prominent accumulation and others showing little to no inflammatory cell accumulation even when the same laser was applied. Initially, the cause of this variability was unclear.

At that time, there were reports indicating that hepatocytes in the portal vein (PV) region and the central vein (CV) region of the liver have distinct functions. Based on this, we hypothesized that local inflammation in the liver might also differ between the PV and CV regions. To test this, we established an experimental system that distinguishes between PV and CV regions and performed laser ablation separately in each. As a result, we discovered that while inflammation was induced in the CV region in response to identical laser irradiation, less inflammation occurred in the PV region [Figure 8]. This indicated that the initial variability in our results was due to differences in the irradiated regions. Furthermore, when macrophages (Kupffer cells) in the liver were depleted by administering clodronate-encapsulated liposomes, laser-induced inflammation was also observed in the PV region, just as in the CV region [Figure 1]. These findings suggest that macrophages with inflammation-suppressing properties are uniquely present only in the PV region.

Next, we sought to identify the "immune-suppressive macrophages present only in the PV region." However, since the PV and CV regions are intermingled within liver tissue, isolating cells exclusively from the PV region was a physically extremely challenging task. To address this, we combined in vivo imaging with photoactivatable (PA)-GFP (a GFP that is off in its steady state but turns on when exposed to light in the violet spectrum) to establish a unique cell recovery method. By selectively photoactivating PA-GFP in the PV and CV regions of the liver of mice expressing PA-GFP throughout the body, we marked cells in each region with GFP, recovered cells from the liver, and sorted them based on GFP positivity, successfully recovering cells from the PV and CV regions individually. As a result, it was revealed that macrophages in the PV region, unlike those in the CV region, highly express Marco, a scavenger receptor for DAMPs (which internalize and inactivate them), and secrete the immunosuppressive cytokine IL-10 (the immunosuppressive macrophages in the PV region are referred to as MP2 (Macrophage type 2) in this paper).

In this study, we further demonstrated that MP2 is dependent on intestinal bacteria for its steady influx from the intestine to the hepatic portal vein area, and identified Odoribacteraceae as a bacterial species particularly prone to inducing MP2 production. Furthermore, by disrupting MP2 function through Marco deficiency, we demonstrated that inflammation is more easily induced in the liver. Using mouse models and human clinical samples, we also proved that MP2 levels are reduced in liver inflammatory diseases such as metabolic dysfunction-associated steatohepatitis (MASH) and primary sclerosing cholangitis (PSC). The liver is exposed to a constant influx of "contaminants" such as

intestinal bacteria, their components, and absorbed nutrients via the portal vein from the intestines, creating a potentially inflammatory environment. However, inflammation does not typically occur in the liver, leading to the assumption that a unique "immune tolerance" system exists there. Our findings clarify the cellular basis of this liver immune tolerance system. This finding suggests that disruption of this system may lead to the onset of chronic inflammatory liver diseases, thereby highlighting its significant medical implications [Figure 2]

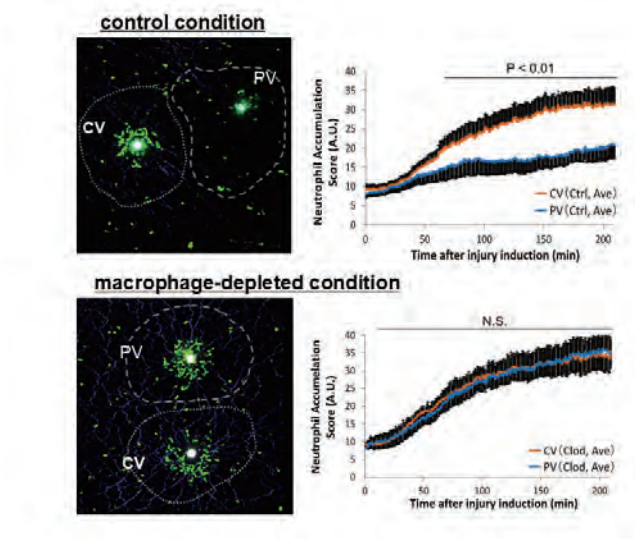

Figure 1.
Variability in inflammatory response to laser ablation in the liver. (Left) Inflammation induced by laser ablation. (Right) Significant inflammation (left) and mild inflammation (right) in response to the same stimulus.

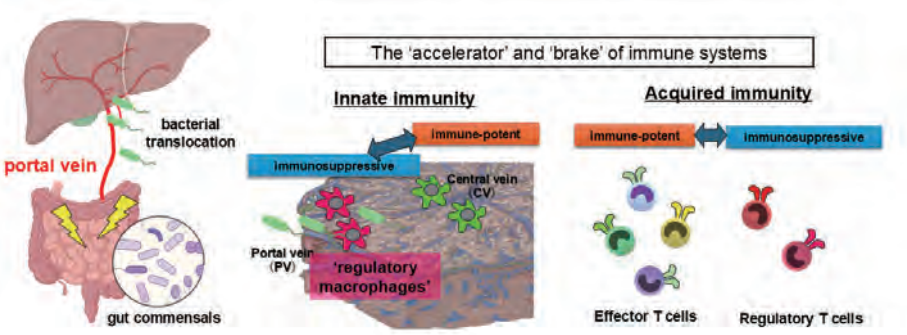

Figure 2.
The nature of immune tolerance in the liver and the significance of the "regulatory" innate immune system. (Left) The liver requires an immune tolerance mechanism because blood containing intestinal bacteria, nutrients, and other contaminants enters the liver via the portal vein from the intestines. (Right) The accelerator and brake of the immune system. In the adaptive immune system, the TCR repertoire differs between activated and suppressed cells, while in the innate immune system, the mechanisms are distinguished by the sites where they act.

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1. Miyamoto Y, Kikuta J, Matsui T, Hasegawa T, Fujii K, Okuzaki D, Liu Y-C, Yoshioka T, Seno S, Motooka D, Uchida Y, Yamashita E, Kobayashi S, Eguchi H, Morii E, Tryggvason K, Shichita T, Kayama H, Atarashi K, Kunisawa J, Honda K, Takeda K, Ishii M. Periportal macrophages protect against commensal-driven liver inflammation. Nature, 629: 901–909 (2024).

2. Shimizu K, Kikuta J, Ohta Y, Uchida Y, Miyamoto Y, Morimoto A, Yari S, Sato T, Kamakura T, Oshima K, Imai R, Liu Y-C, Okuzaki D, Hara T, Motooka D, Emoto N, Inohara H, Ishii M. Single-cell transcriptomics of human cholesteatoma identifies an activin A-producing osteoclastogenic fibroblast subset inducing bone destruction. Nat. Commun., 14(1):4417 (2023).

3. Taniguchi S, Matsui T, Kimura K, Funaki S, Miyamoto Y, Uchida Y, Sudo T, Kikuta J, Hara T, Motooka D, Liu Y-C, Okuzaki D, Morii E, Emoto N, Shintani Y, Ishii M. In vivo induction of activin A-producing alveolar macrophages supports the progression of lung cell carcinoma. Nat Commun. 14(1):143 (2023).

Chemical Imaging Techniques

Kazuya Kikuchi, PhD

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Postdoctoral Fellow	1
Research Assistant	1
Support Staff	2

Light-Activated Gene Expression System Using a Caging-Group-Free Photoactivatable Dye

Optogenetics and photochemical tools have revolutionized the ability to control biological processes with high spatial and temporal precision. Optical regulation of transcription using chemical compounds is an effective strategy to manipulate gene expression spatiotemporally. Traditional methods often rely on "caged" compounds, molecules rendered inactive by photoremovable protecting groups (PPGs) that activate by light illumination. However, these methods have limitations. The activation of caged compounds requires intense UV light exposure, which can damage cells and tissues. Moreover, the removal of PPGs can release potentially toxic byproducts. Furthermore, the states of effector molecules cannot be visually distinguished, making it impossible to monitor the activity state of the effector molecules. To overcome these challenges, we developed a novel optical system with caging-group-free photoactivatable fluorophore, utilizing visible light for activation and minimizing cytotoxic effects.

We focused on PaX_{560} as a caging-group-free photoactivatable dye. This dye undergoes a traceless photoconversion upon exposure to visible light without releasing toxic byproducts. Moreover, the photoconversion changes its charge state from a neutral Si-xanthone dye to a cationic Si-pyronine dye. Since Si-pyronine dye emit fluorescence, the activation state of the effector molecules can be distinguished. We employed the positive charge acquisition to optically regulate the activity of a multidrug-binding transcriptional regulator, QacR. QacR is a multidrug-binding transcriptional repressor from *Staphylococcus aureus*. It binds to operator DNA sequences, IR1, inhibiting transcription. Upon binding to a range of cationic lipophilic dyes, the repression activity of QacR is mitigated, resulting in transcriptional activation.

PaX_{560} and its photoconverted form (PaX_{560}-CF) were synthesized according to the previous literature. The absorbance measurement at 560 nm revealed that the photoconversion is completed by mild irradiation of 3 mW/cm^2 at 405 nm for 1 min. The binding property to QacR was examined by using isothermal titration calorimetry (ITC). The binding assay showed PaX_{560} does not bind to QacR while its cationic form can bind with micromolar dissociation constant, indicating the dye photoconversion induces the binding to QacR. Next, a P_{T7}/QacR promoter system was constructed by combining T7 promoter sequence to QacR binding sequence. The sequence was optimized by mRNA production with in vitro T7 transcription assay. Using the optimized sequence construct, mRNA production was evaluated in the system using a PaX_{560} dye with light illumination at 405 nm. the transcribed RNA was increased by ~20-fold upon low-intensity light illumination to activate PaX_{560}. These results demonstrated the photoactivated PaX_{560}-CF induced detachment of QacR from the binding sequence to permit RNA synthesis by T7 RNA polymerase.

Finally, this P_{T7}/QacR promoter system was installed into *E. coli* BL21(DE3), one of the most commonly used bacterial strains for recombinant protein production in the field of biotechnology. Light-regulated gene activation was demonstrated using bacterial luciferase (LuxCDABE) or fluorescent protein (sfGFP) as a reporter. After installation of the expression system into *E. coli* BL21(DE3), the expression level of luciferase or green fluorescent protein reporter was controlled by light with low-intensity and short exposure time. Furthermore, the activity state of PaX_{560} dye was simultaneously visualized by fluorescence imaging.

In conclusion, a novel class of optochemical transcriptional regulation system was developed using a photoactivatable dye and QacR as a transcriptional regulator. The key driver of this system is the light-induced charge transition from neutral PaX_{560} to its positively charged form. Our P_{T7}/QacR promoter system was demonstrated through in vitro transcription assay and luciferase / fluorescence reporter assay in live bacteria. This system can serve as a powerful biobrick component for developing artificial genetic circuits.

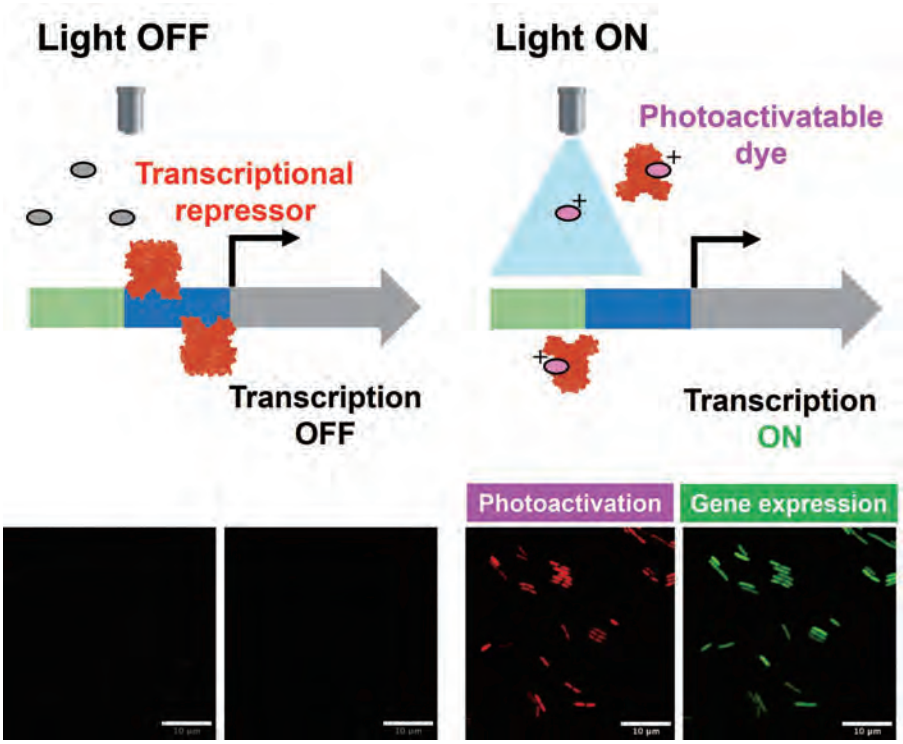


Figure.
(top) Schematic of the light-activated transcription system using the photoactivatable dye PaX_{560} and the IR1 operator-binding factor QacR as a transcription regulator. (bottom) Fluorescence imaging of photoactivation of PaX_{560} and sfGFP expression without (left) and with (right) light irradiation in *E. coli*. Scale bar: 10 μm.

Recent Publications

1. Nonomura T, Minoshima M, Kikuchi K. Light-Activated Gene Expression System Using a Caging-Group-Free Photoactivatable Dye. *Angew Chem. Int. Ed.* 64:e202416420 (2024).

2. Wu Y, Minoshima M, Kikuchi K. Development of Elliptic Core-shell Nanoparticles with Fluorinated Surfactants for ^{19}F MRI. *Front Chem.* 1:1408509 (2024).

3. Kamikawa T, et al. Bioisostere-conjugated Fluorescent Probes for Live-cell Protein Imaging without Non-specific Organelle Accumulation. *Chem Sci.* 15:8097-8105 (2024).

4. Hashimoto R, Minoshima M, Kikuchi K. Rational Design of Hydroxylated Thiazole Orange Photocages for Green Light-Triggered DNA Recombination. *ChemBioChem*. 25:e202300799 (2024).

5. Konishi Y, Otera Y, Minoshima M, Kikuchi K. Activatable ^{19}F MRI Probe for Detection of α-amylase Activity. *Chem Lett*. 53:upae003 (2024).

Immune Response Dynamics

Kazuhiro Suzuki, MD/PhD

Professor	Kazuhiro Suzuki
Assistant Professor	Akiko Nakai Taiichiro Shirai
Research Assistant	1
Visiting Scientist	1
Support Staff	2

Our research focuses on uncovering novel mechanisms that regulate lymphocyte migration and elucidating their physiological and pathological significance. In our previous work, we demonstrated that adrenergic neuronal input to the β_2-adrenergic receptor expressed on lymphocytes enhances the responsiveness of specific chemokine receptors and inhibits lymphocyte egress from lymph nodes (Nakai et al., *J. Exp. Med*. 2014). This mechanism was shown to drive diurnal variations in lymphocyte numbers within lymph nodes and, consequently, modulate the magnitude of adaptive immune responses in synchrony with the circadian oscillation of adrenergic neuron activity (Suzuki et al., J. Exp. Med. 2016). These findings provided key insights into the molecular basis of neuroimmune interactions.

In the course of exploring the mechanism underlying the crosstalk between the β_2-adrenergic receptor and chemokine receptors, we identified a protein complex composed of copper metabolism MURR1 domain-containing proteins COMMD3 and COMMD8 (the COMMD3/8 complex) as a positive regulator of chemokine receptor signaling. Our study revealed that the COMMD3/8 complex plays an essential role in the migration of B cells and the induction of humoral immune responses (Nakai et al., *J. Exp. Med*. 2019). However, the contribution of the COMMD3/8 complex to the pathogenesis of immunological disorders remained unclear.

Given the importance of the COMMD3/8 complex in humoral immunity, we investigated its involvement in collagen-induced arthritis, a B cell-dependent murine model of rheumatoid arthritis. Conditional deficiency of the COMMD3/8 complex at the onset of disease attenuated arthritis progression, which was associated with a diminished humoral immune response to collagen. These results indicated that the COMMD3/8 complex contributes to the pathogenesis of collagen-induced arthritis (Shirai et al., *Sci. Immunol*. 2023).

Prompted by these findings, we conducted a chemical screen to identify inhibitors of the COMMD3/8 complex that might serve as therapeutic agents for autoimmune diseases. As the function of the complex depends on the physical interaction between COMMD3 and COMMD8, we searched for compounds that disrupt this interaction. Screening a chemical library enriched in natural products led to the identification of celastrol as the most potent compound (Figure). Celastrol, a bioactive molecule derived from the medicinal herb *Tripterygium wilfordii*, possesses known anti-inflammatory properties, though its mechanism of action had remained poorly understood. Our results demonstrated that celastrol disrupts the COMMD3/8 complex both in live cells and in its purified form, indicating that the compound directly targets the complex. Using site-directed mutagenesis, molecular dynamics simulations, and liquid chromatography–tandem mass spectrometry, we revealed that celastrol covalently binds to cysteine 170 (C170) of COMMD3, leading to dissociation of the complex (Shirai et al., *Sci. Immunol*. 2023).

We next investigated whether celastrol mimics the functional effects of COMMD3/8 complex deficiency. Celastrol inhibited B cell chemotaxis both in vitro and in vivo, and suppressed antibody responses by reducing the formation of germinal center B cells and plasma cells. Notably, celastrol treatment initiated at the onset of collagen-induced arthritis effectively prevented disease progression. These findings demonstrated that celastrol

phenocopies COMMD3/8 complex deficiency, suggesting that the complex is a functional target of celastrol in humoral immunity and autoimmunity.

To further validate this mechanism, we generated a knock-in mouse strain expressing a COMMD3 mutant (C170A) that is resistant to celastrol while retaining its biological function. B cells isolated from *Commd3*^{C170A} mice were fully resistant to celastrol-induced inhibition of chemotaxis. Moreover, celastrol treatment failed to suppress humoral immune responses and collagen-induced arthritis in these mice. These results confirmed that the COMMD3/8 complex is a principal target of celastrol (Shirai et al., *Sci. Immunol.* 2023).

Our study highlights the involvement of the COMMD3/8 complex in the progression of antibody-mediated autoimmune disease. However, the precise point at which this complex acts in the pathogenesis of autoimmunity remains to be clarified. Additionally, as most of our findings were derived from murine models, the relevance of the COMMD3/8 complex to human autoimmune diseases has yet to be established. Future studies will address these challenges and aim to develop novel therapeutic strategies targeting the COMMD3/8 complex in immune-mediated disorders.

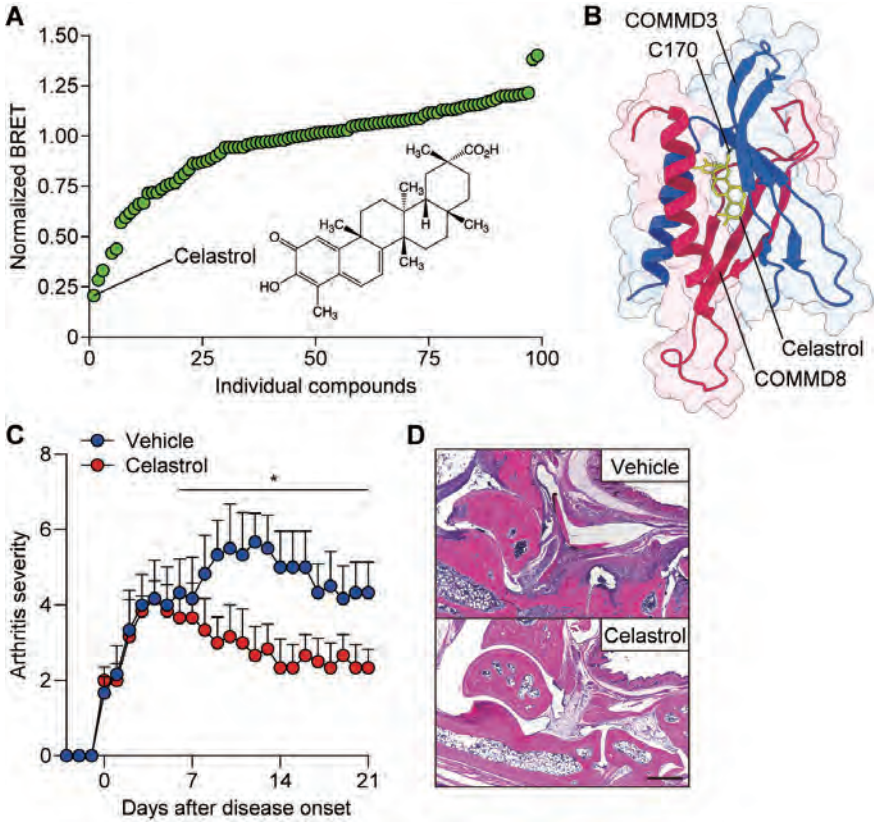


Figure.
Celastrol inhibits the COMMD3/8 complex and alleviates autoimmunity. (**A**) Identification of celastrol as a COMMD3/8 complex inhibitor. (**B**) An *in silico* model of the interaction of celastrol and the COMMD3/8 complex. (**C** and **D**) Effects of celastrol on the severity (C) and histopathology (D) of collagen-induced arthritis. Scale bar, 500 µm.

Recent Publications

1. Shirai T, Nakai A, Suzuki, K. Chemoattractant receptor signaling in humoral immunity. Int Immunol. 36:429-438 (2024).

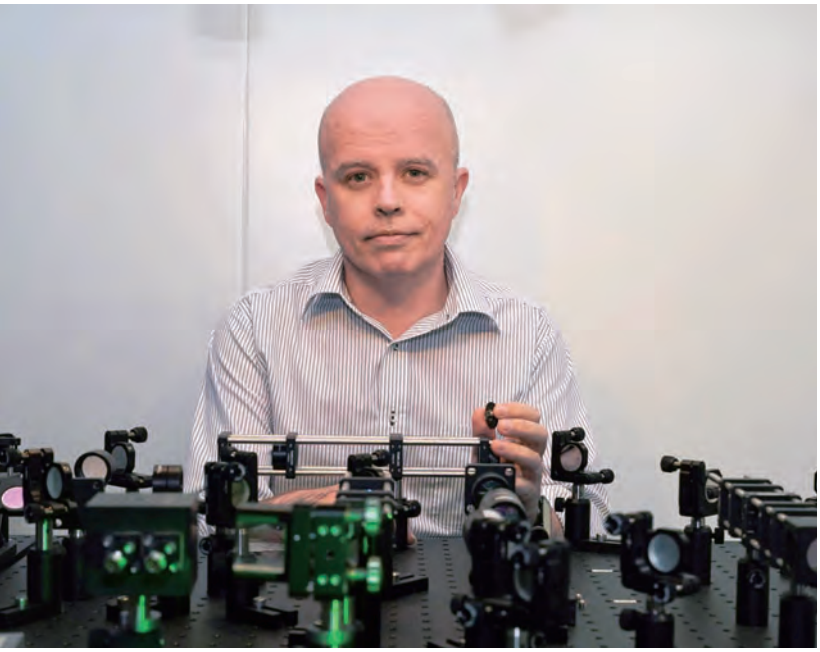
2. Shirai T, Nakai A, Ando E, Fujimoto J, Leach S, Arimori T, Higo D, van Eerden FJ, Tulyeu J, Liu Y-C, Okuzaki D, Murayama MA, Miyata H, Nunomura K, Lin B, Tani A, Kumanogoh A, Ikawa M, Wing JB, Standley DM, Takagi J, Suzuki K. Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex. Sci Immunol. 8: eadc9324 (2023).

3. Nakai A, Fujimoto J, Miyata H, Stumm R, Narazaki M, Schulz S, Baba Y, Kumanogoh A and Suzuki K. The COMMD3/8 complex is a determinant of GRK6 specificity for chemoattractant receptors. J Exp Med. 216:1630-1647 (2019).

4. Suzuki K, Hayano Y, Nakai A, Furuta F and Noda M. Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes. J Exp Med. 213:2567-2574 (2016).

5. Nakai A, Hayano Y, Furuta F, Noda M and Suzuki K. Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors. J Exp Med. 211:2583-2598 (2014).

Biophotonics



Nicholas Isaac Smith, PhD

Associate Professor	Nicholas Isaac Smith
Assistant Professor	Alison Hobro
Visiting Scientist	1

The Biophotonics laboratory develops tools for label-free analysis of single cells. Single-cell analysis is a popular target for a variety of research fields, usually pursued by labeling surface markers, by introducing fluorescent dyes into the cell, or by invasive, yet comprehensive, techniques such as single cell RNA sequencing. In contrast, our tools are based on label-free optical methods, which aim to produce some of the same discriminatory capability as the more invasive methods. Additionally, label-free methods are based on endogenous contrasts of the cell, and can also find novel features that can be used to discriminate between cell phenotypes or cell states.

We completed a several-year long project aimed at developing a non-invasive approach to identify regulatory T cells (Tregs) using Raman spectroscopy combined with machine learning. Tregs play a crucial role in maintaining immune tolerance and preventing autoimmune diseases. Traditionally, identifying these cells requires invasive labeling methods, such as intracellular staining for the Foxp3 marker, or reliance on surrogate surface markers that can be inaccurate and disrupt cell function. By applying our label-free Raman spectroscopy technique that uses intrinsic molecular vibrations, coupled with machine learning analysis (by LASSO logistic regression), we were able to accurately differentiate Tregs from conventional T cells (Tconv). Although Raman spectra from Tregs and Tconv appeared visually similar, statistical models could reliably identify Raman markers discriminating Tregs with high accuracy—as high as 92%. This level of accuracy is competitive with conventional labelled techniques, and we also successfully identified Tregs across independent donors, demonstrating robust clinical potential. The label-free measurement approach offers critical advantages, such as preserving cell viability, avoiding functional disruptions from labeling, and enabling repeated analyses of live cells. Additionally, it provides molecular-level insight into the intrinsic biochemical differences between cell types, particularly regarding protein structures and nucleic acids, without external interference. Without assumptions or knowledge of Treg subtypes, our approach was able to identify a sub-population which has been recognized in the field as Fraction III.

While the current throughput is limited compared to flow cytometry (~1000 cells/hour), the amount of data generated is vastly higher than in typical label-free studies, allowing robust statistical analysis. We could then extract biochemical markers, revealing the molecular basis of the discrimination model. This showed that the primary differences between Tregs and Tconv was related to protein structure bands (beta sheet and alpha helix ratios) and some specific amino acids such as tryptophan and phenylalanine. We also found that individual human donors had characteristic population-level features so that a sub-sample of human Treg and Tconv cells can be traced back to each individual donor. Overall, the use of Raman spectroscopy as a non-invasive, label-free detection technique for Tregs is an exciting advance toward clinical applications, potentially revolutionizing immune cell analysis and improving therapeutic strategies for autoimmune diseases.

In the above study, we used label-free methods to characterize phenotypes where labelling is possible, but not desirable. In the next project, we used our technology in applications where staining does not have suitable performance, and Raman-based classification is ideal. A significant challenge in immunology is

how to distinguish neutrophil extracellular trap (NET) based cell damage from necrotic cell death. Traditional methods including DNA staining and ELISA do not have sufficient sensitivity to distinguish between them since both types of cell damage include similar morphological and biochemical changes. Our Raman analysis was able to clearly distinguish between necrotic changes and NET-related changes, with additional insight into which type of NET-producing stimulant had been applied at the single-cell level. This work highlighted the improvement that Raman microscopy provides, not only in improving accuracy in NET identification, but also providing insight into the subtle biochemical variations between different cell death pathways, which is important for studying NET biology and potentially diagnosing diseases where NET formation plays a crucial role.

We also published findings on optimizing single cell analysis, on liver-related changes in NASH, and worked with our collaborators towards Raman/Fluorescence cryoimaging, and comprehensive elucidation of lipid nanoparticle uptake in mRNA vaccines.

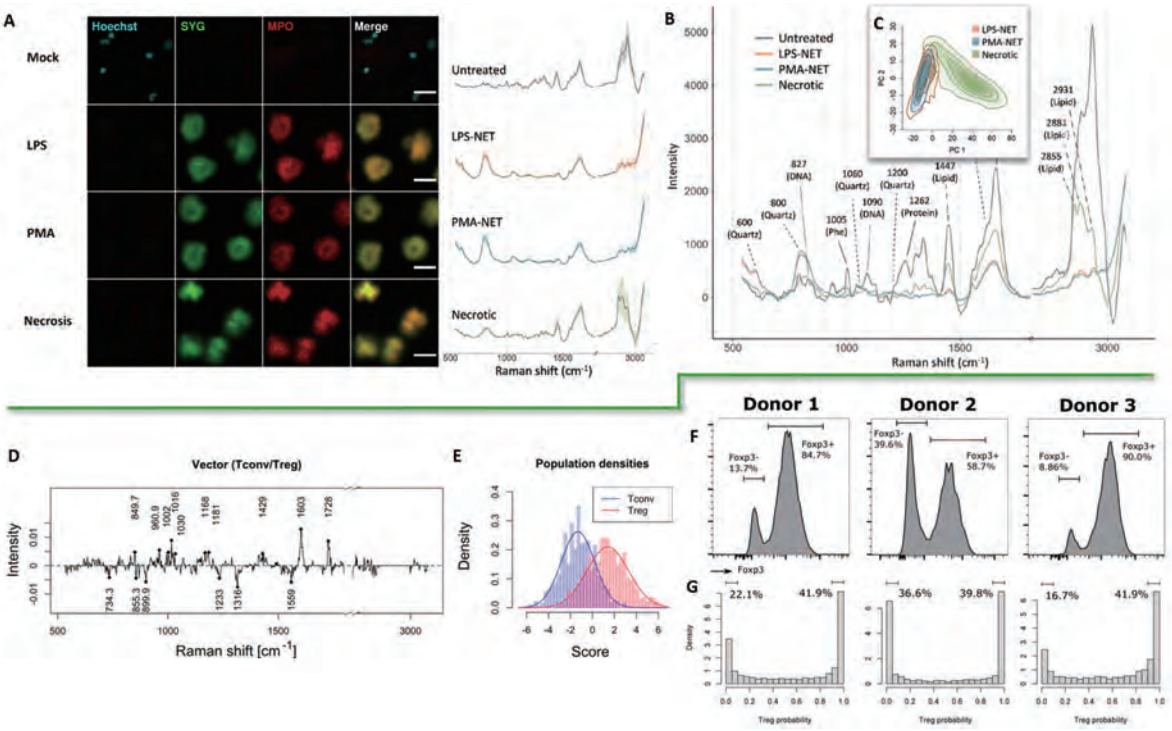


Figure.
Recent results using Raman microscopy and single-cell analysis. Panel A shows neutrophils treated with a range of chemicals that include either NET formation or necrosis, imaged with typical stains. Although the morphology in necrosis is evident, the stains do not have selectivity for these widely different cell damage conditions. B shows single cell Raman analysis, where even inspection by eye shows a marked difference between NETs and necrosis. C shows simple PCA analysis, where the biochemical differences can easily discriminate between the cell treatments. Going further it is possible to detect subtle biochemical differences between LPS and PMA-induced NETs, hinting at their distinct response pathways (Lelliott *et al* 2023). Highly accurate label-free detection of Treg cells was also achieved, allowing us to find characteristic differences to Tconv cells (D), and assess the populations of each in human and murine samples (E). The label-free phenotype assessment has the advantage of not using a marker that binds to Foxp3, and retains similar discrimination sensitivity (F). The label-free measurement and machine learning resulting in binomial distributions with characteristic features that allow us to link measured cells with their human donor (G).

Recent Publications

1. Mizushima K, et al. Raman microscopy of cryofixed biological specimens for high-resolution and high-sensitivity chemical imaging. Science Adv. (2024) in press.

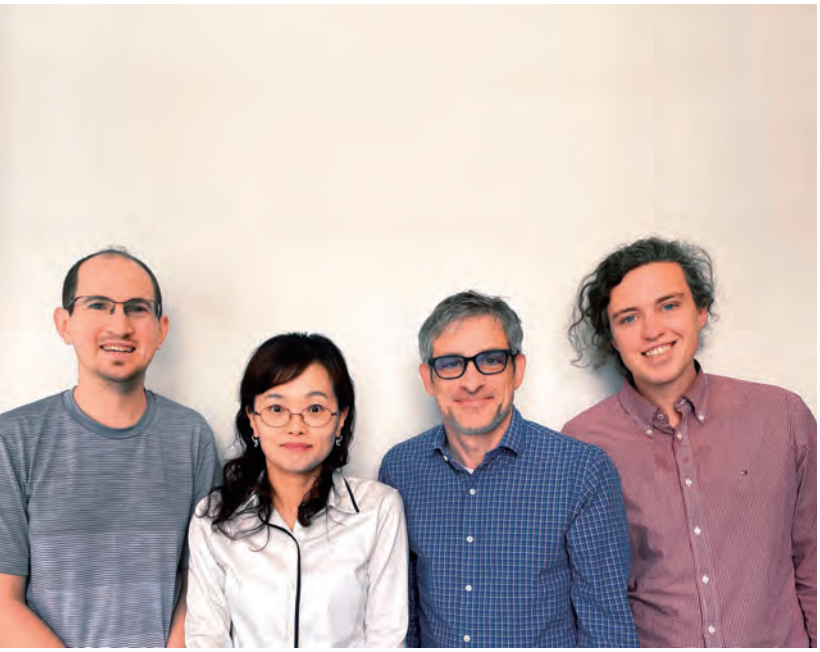
2. Hobro AJ, Sakaguchi T, Akira S, Smith NI. Correlative quantitative Raman chemical imaging and MCR-ALS in mouse NASH model reveals direct relationships between diet and resultant liver pathology. Chemical & Biomedical Imaging 2 (8):577–583 (2024).

3. Hobro AJ, et al. Imaging vs non-imaging Raman spectroscopy for high-throughput single-cell phenotyping. Anal Chem. (2024).

4. Pavillon N, Lim EL, Tanaka A, Hori S, Sakaguchi S, Smith NI. Non-invasive detection of regulatory T cells with Raman spectroscopy. Sci Rep. 14 (1):14025 (2024).

5. Lelliott PM, et al. Single-cell Raman microscopy with machine learning highlights distinct biochemical features of neutrophil extracellular traps and necrosis. Sci Rep. 13 (1):10093 (2023).

Systems Immunology



Daron Standley, PhD

Professor	Daron Standley
Associate Professor	Kazutaka Katoh
	Songling Li
	Soyoung Park
Assistant Professor	Arthur Millius
	Hendra Ismanto
Visiting Scientist	3

Classification of health/disease from Adaptive Immune Receptors

We have formulated the problem of disease diagnosis from Adaptive Immune Receptors (AIRs) as a classification problem that can be solved by ML. The classifier, MyImmune, required the development of a more useful representation of AIRs than the conventional "clonotype" definition, that could group AIRs from different individuals (Fig. 1A). The resulting clusters were found to be >95% specific in terms of targeted antigens (Fig. 1B). We then validated MyImmune on three classes of disease: infectious (COVID-19, HIV), autoimmune (Autoimmune Hepitaitis, Type-1 diabetes) and cancer (non-small cell lung cancer, colorectal cancer). MyImmune demonstrated significant improvement over seven alternative classifiers using the same inputs: mean ROC AUC 0.893 vs 0.777, respectively. Moreover, we observed linear improvement on MyImmune's performance with the size of the training data (Fig. 1C). A surprising finding for cancer is that healthy individuals harbor a reservoir of potential tumor-infiltrating lymphocytes that can be identified by MyImmune feature importance.

Activation of Immune Responses by Inhibition of Regnase-1–Mediated RNA Decay

Regnase-1 is an essential RNase that inhibits immune cell activation in both innate and adaptive immune cells by targeting the mRNA of pro-inflammatory cytokines, including interleukin 6 (IL6). Although genetic suppression of Regnase-1 activity in CD8+ T cells and NKT cells has been shown to enhance antitumor immunity, no inhibitors of Regnase-1 that activate immune responses have been identified to date. We recently established a spectral shift assay to investigate the binding interactions between Regnase-1 and its RNA substrates and further developed a spectral shift-based ligand displacement assay to evaluate whether nucleic acid analogs can function as competitors to disrupt Regnase-1–RNA interactions. By exploiting a library of nucleic acid analogs and this RNA displacement assay, we identified multiple candidate competitors of Regnase-1 RNA substrates. We found an inhibitor and several of its derivatives that displaced Regnase-1 substrates with submicromolar affinity, inhibited Regnase-1–mediated degradation of Il6 mRNA in vitro, and enhanced Il6 mRNA levels in mouse embryonic fibroblasts. The 2.62 Å crystal structure revealed that the inhibitor is bound to the Regnase-1 active site, coordinating with the catalytic Mg2+. Taken together, these data establish the first small-molecule inhibitor of Regnase-1–mediated RNA decay and suggest a novel mode of pharmacologically activating immune responses.

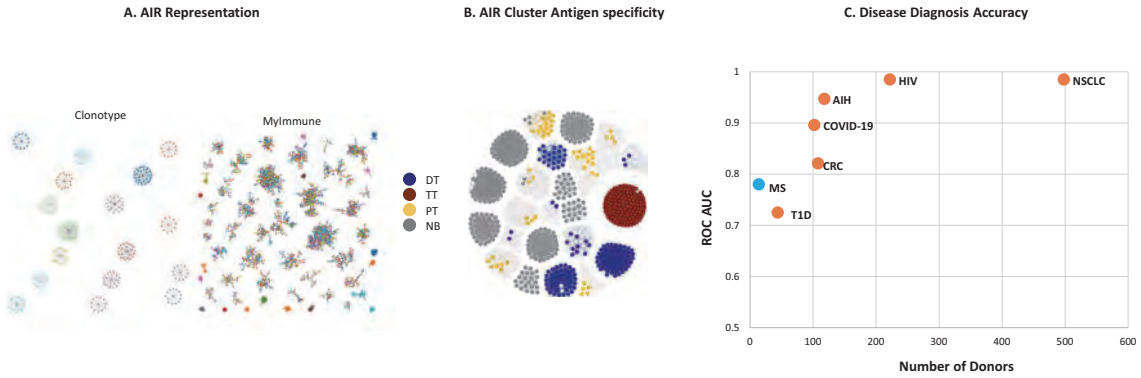


Figure 1.
MyImmune Disease Classification. **A**, B cell receptor (BCR) heavy chain networks were constructed for 10 COVID-19 patients; in these networks, nodes are colored by donor, and edges represent clonotype or MyImmune similarity. Clonotype networks are typically small and do not connect different donors. MyImmune networks are much larger and generally connect many donors. **B**, BCR networks derived from single-cell immune profiling of diphtheria-tetanus-pertussis (DTP)-vaccinated donors were demonstrated by ELISA to exhibit 96% antigen purity, surpassing the apparent 82% purity achieved by assigning antigens to the same B cells using fluorescently labeled DTP antigen probes. **C**, The performance of MyImmune on new indivuduals (i.e. not seen by the ML training) was benchmarked for six diseases in three categories using the Area Under the Receiver Operating Characteristic Curves (ROC AUC). The MyImmune performance increased linearly with the number of donors up to a threshold value of ~200, after which the classifier was nearly perfect.

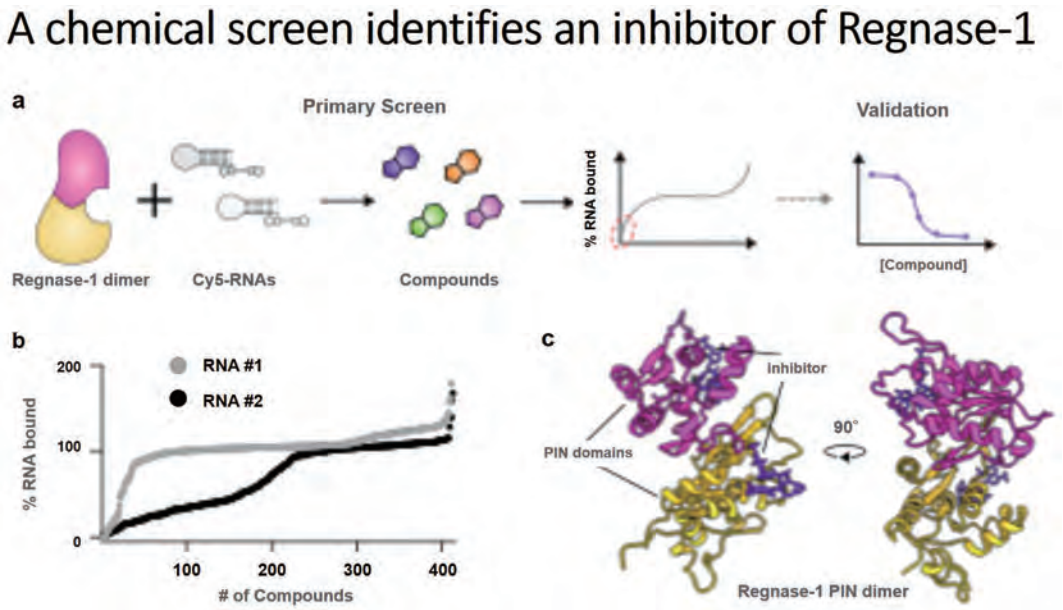


Figure 2.
a, Chemical inhibitor screening workflow. **b**, Summary of the primary screen. Normalized values of fraction of Cy5-labeled RNA #1 (gray) and RNA #2 (black) bound to Regnase-1 NPZC treated with compound versus Regnase-1-RNA complex treated with DMSO. **c**, Two views of the model of Regnase-1 PIN-inhibitor complex. The PIN dimer consists of one PIN monomer (yellow) bound in a head-to-tail orientation to the other PIN monomer (pink). An inhibitor molecule (purple) binds to a Mg2+ ion (gray) at the active site of each PIN monomer.

Recent Publications

1. Saputri DS, et al. Deciphering the antigen specificities of antibodies by clustering their complementarity determining region sequences. mSystems 8:e0072223 (2023).

2. Millius A, et al. Circadian ribosome profiling reveals a role for the Period2 upstream open reading frame in sleep. Proc Natl Acad Sci U S A. 120:e2214636120 (2023).

3. Mitsui Y, et al. Expression of the readthrough transcript CiDRE in alveolar macrophages boosts SARS-CoV-2 susceptibility and promotes COVID-19 severity. Immunity 56:1939-1954. (2023).

4. Kitagawa Y, et al. Construction of a T cell receptor signaling range for spontaneous development of autoimmune disease. J Exp Med. 220 (2023).

5. Eerden FJv, et al. TCR-pMHC complex formation triggers CD3 dynamics. eLife in press, 2022.2007.2027.501668 (2023).

Statistical Immunology

Yukinori Okada, MD/PhD

Professor	Yukinori Okada
Assistant Professor	Yuya Shirai
Research Assistant	3
Support Staff	1

1. Goal of Our Laboratory

Our laboratory is dedicated to uncovering how individual genetic differences contribute to the risk of immune-related diseases. By leveraging large-scale human genomic and multi-omics datasets, we aim to develop innovative statistical and computational frameworks to identify causal genetic factors. This approach—situated within the emerging field of statistical immunology—bridges genomics, bioinformatics, and immunology to provide new insights into disease mechanisms. Ultimately, our goal is to generate tools and knowledge that can guide precision medicine for complex immune disorders.

2. Single-Cell Analysis of X Chromosome Inactivation Escape

In female cells, one of the two X chromosomes is typically silenced to ensure dosage compensation. However, some genes manage to "escape" this inactivation, and the extent of such escape appears to differ across cell types and tissues. To study this phenomenon in greater detail, we developed a computational tool called scLinaX, which enables the quantification of gene expression specifically from the inactive X chromosome using droplet-based single-cell RNA sequencing data.

Using scLinaX, we discovered that lymphocytes exhibit a higher level of X inactivation escape than myeloid cells. We further expanded this approach to include chromatin accessibility through a multiomic extension, scLinaX-multi, confirming similar escape patterns at the epigenetic level. Analyzing datasets from multiple human organs, we found that tissues rich in lymphoid cells consistently showed stronger escape signals. These findings underscore a cell-type- and tissue-specific regulation of X inactivation. Comparative analysis of genome-wide association study (GWAS) results between males and females revealed that XCI escape may shape sex-specific genetic effects on complex traits.

3. Population-Scale Proteogenomics of HLA Genes

To investigate how genetic variation influences protein expression, particularly for genes central to the immune system such as the HLA family, we performed a large-scale analysis combining genotyping, transcriptomics, and plasma proteomics. This study was conducted in collaboration with the Japan COVID-19 Task Force, encompassing thousands of participants. We conducted high-resolution mapping of cis-eQTLs and cis-pQTLs and found that mRNA and protein regulation often diverge, due in part to the complex origin of plasma proteins and distinct regulatory mechanisms. For example, many pQTLs were linked to structural variants, especially in extracellular domains, while eQTLs were often located in noncoding regulatory regions. Interestingly, variation in HLA class I alleles was associated with the expression of KIR genes, which play a key role in innate immunity. Expression levels of the ABO gene showed an inverse relationship between RNA and protein, driven by different genetic variants. These findings highlight the importance of integrating multi-layer omics data to understand immune gene regulation at the population level.

4. Uncovering Viral Links to Autoimmune Diseases

To explore the impact of persistent viral elements on human health, we analyzed whole-genome sequencing data from over 6,000 Japanese individuals, including patients with autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis, as well as COVID-19 patients and

healthy controls. Our analysis focused on two key components of the blood DNA virome: endogenous HHV-6 (eHHV-6) and anelloviruses. We found that individuals carrying integrated eHHV-6B sequences had a significantly higher risk for SLE and pulmonary alveolar proteinosis, and these findings were replicated in an independent cohort. Integration sites were mapped to chromosome 22q using long-read sequencing, and single-cell transcriptomics revealed that eHHV-6B presence is linked to a distinctive immune activation profile in SLE patients. In parallel, we observed that an elevated load of anelloviruses was associated with SLE, rheumatoid arthritis, and COVID-19, suggesting a broader role for the virome in modulating immune responses. These results demonstrate the potential contribution of latent viral elements to autoimmune and infectious disease risk, opening new avenues for understanding host-pathogen interactions in complex diseases.

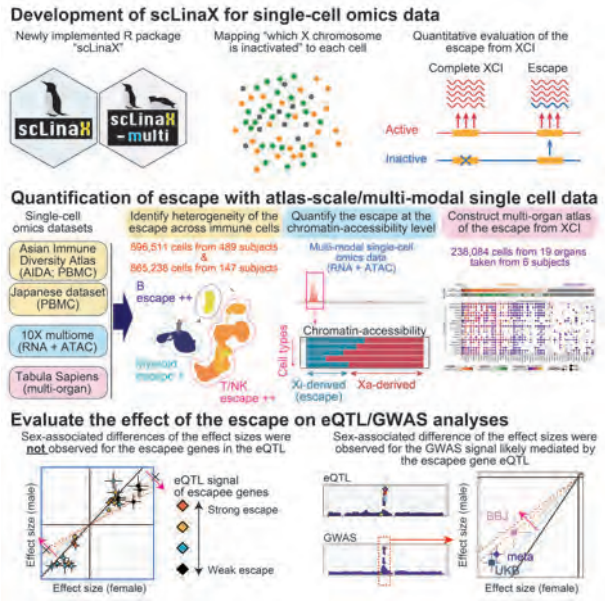


Figure 1.
scLinax, bioinformatics tool to investigate to quantify X chromosome inactivation escape in a single cell resolution.

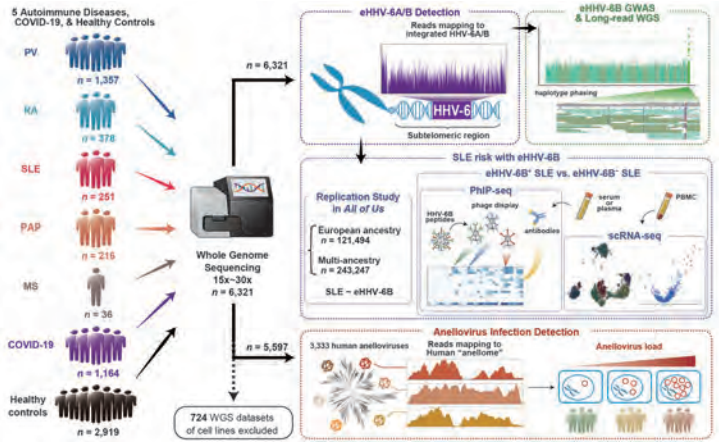


Figure 2.
Quantification of endogenous and exogenous virome by utilizing non-human reads in human whole-genome sequencing.

Recent Publications

1. Sonehara K, et al. Germline variants and mosaic chromosomal alterations affect COVID-19 vaccine immunogenicity. *Cell Genom* 5:100783 (2025).
2. Yata T, et al. Contribution of germline and somatic mutations to risk of neuromyelitis optica spectrum disorder. *Cell Genom* 5:100776 (2025).
3. Sasa N, et al. Blood DNA virome associates with autoimmune diseases and COVID-19. *Nat Genet*. 57:65-79 (2025).
4. Wang QS, et al. Statistically and functionally fine-mapped blood eQTLs and pQTLs from 1,405 humans reveal distinct regulation patterns and disease relevance. *Nat Genet*. 56:2054-2067 (2024).
5. Tomofuji Y, Edahiro R, et al. Quantification of escape from X chromosome inactivation with single-cell omics data reveals heterogeneity across cell types and tissues. *Cell Genom*. 4:100625 (2024).

Quantitative Immunology

Associate Professor Diego Diez

Our group applies computational and single cell genomics techniques to understand the immune system. We develop computational methods to analyze single cell data. We integrate experimental data, including transcriptome, chromatin accessibility, protein expression, immune repertoire, and spatial genomics, with publicly available information into network models of immune regulation. We apply this framework to study gene regulatory networks controlling immune cell development and function.

Development of computational methods

- An important problem in single cell genomics is how to combine different datasets while correcting for batch effects. A key focus is on preserving the original cell population structure while not introducing bias. We developed Canek, a method that leverages a fuzzy logic framework to perform efficient batch correction or replicated experiments without bias.
- Another problem is the identification of marker genes. In collaboration with Alexis Vandenbon at Kyoto University, we developed *singleCellHaystack*, a method to efficiently identify differentially active features (i.e., changes in genes, proteins, chromatin accessibility, etc.) from single cell and spatial genomics data in datasets with millions of cells.
- Protein expression levels are classically used to define and identify cell populations. CITE-seq and other genomics methods use barcoded antibodies to simultaneously measure RNA and protein expression at single cell resolution. Because barcoded antibodies are expensive most single cell datasets do not measure proteins. In collaboration with the Human Immunology (Single Cell Genomics) laboratory, we are developing a method that combines probabilistic modeling and deep learning to predict protein expression from RNA expression levels using publicly available CITE-seq data.

Mathematical modeling

The large number of cells obtained in single cell genomics experiments opens the door to approaches that study the immune system using mathematical modeling and machine learning. Transcriptional regulatory networks are critical determinants of cell identity and function. We use machine learning to model immune transcriptional regulatory networks. Using the expression level of the regulators as a proxy for their activities we apply these methods to study how transcriptional networks change during immune cell differentiation and disease.

Applications to immunology

Using single cell transcriptomics, protein expression, immune repertoire, and chromatin accessibility we study the differentiation of T cells in the thymus of BALBc and C57BL6 mice. Integration of different datasets with different modalities enables us to understand how changes in regulatory networks during development effect T cell specification. In a clinical setting, we apply single cell genomics (transcriptome, protein expression and immune repertoire) of PBMCs and tonsils to get insight into IgA nephropathy onset and therapies. We use single nuclei multiome (transcriptome and chromatin accessibility) to study sex differences in immune responses to vaccination.

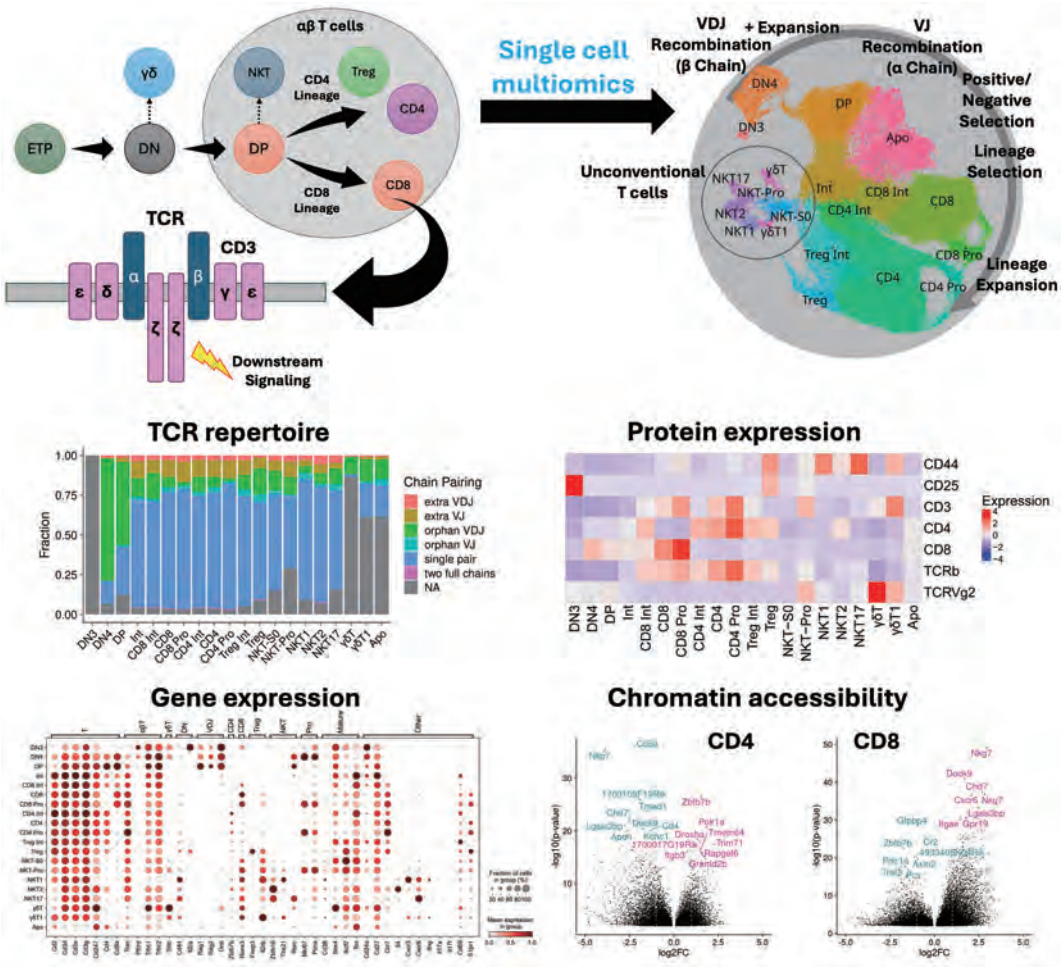


Figure.
Single cell genomics identifies differentiation pathways of developing thymocytes.

Recent Publications

1. Sun X, Nagahama Y, Singh SK, Kozakai Y, Nabeshima H, Fukushima K, Tanaka H, Motooka D, Fukui E, Vivier E, Diez D & Akira S. Deletion of the mRNA endonuclease Regnase-1 promotes NK cell anti-tumor activity via OCT2-dependent transcription of Ifng. Immunity 57:1360-1377 e1313 (2024).

2. Vandenbon A & Diez D. A universal tool for predicting differentially active features in single-cell and spatial genomics data. Sci. Rep. 13:11830 (2023). doi:10.1038/s41598-023-38965-2.

3. Loza M, Teraguchi S, Standley DM & Diez D Unbiased integration of single cell transcriptome replicates. NAR Genom Bioinform 4, lqac022 (2022). doi:10.1093/nargab/lqac022.

4. Diez D, Morte B & Bernal J. Single-Cell Transcriptome Profiling of Thyroid Hormone Effectors in the Human Fetal Neocortex: Expression of SLCO1C1, DIO2, and THRB in Specific Cell Types. Thyroid 31:1577–1588 (2021).

5. Vandenbon A and Diez D. A clustering-independent method for finding differentially expressed genes in single-cell transcriptome data. Nat Commun 11(1):4318 (2020). doi:10.1038/s41467-020-17900-3

Events & Outreach Activities

International Symposium on Microbiology and Immunology

The 14th International Symposium of IFReC

This symposium was co-organized with the Center for Infectious Disease Education and Research (CiDER) at Osaka University, the project for "Self-referential immune perception" (Grant-in-Aid for Transformative Research Areas, JSPS). Centering on basic research achievements relating to microbiology and immunology, this symposium consists of 10 lectures by world-leading scientists. This symposium was a significant opportunity for the participants to share ideas and expertise for further development of microbiology, immunology, and life science.

- **Date:** November 12, 2024
- **Venue :** Special Conference Room, 12th floor,
  Osaka International Convention Center (Grand Cube Osaka)

Speakers (order of presentation)	Title
Katsumori Segawa (Institute of Science Tokyo, Japan)	'Phospholipid asymmetry in the plasma membrane and human diseases'
Satoshi Uematsu (Osaka Metropolitan University, Japan)	'An enterococcal phage-derived enzyme suppresses graft-versus-host disease'
Yasutaka Okabe (IFReC, Osaka University)	'Mucociliary clearance in airway host defense'
Mikael Martino (Monash University, Australia)	'Leveraging the immune system and neuro-immune interactions to promote tissue repair and regeneration'
Kazuyo Moro (IFReC, Osaka University)	'The impact of appendectomy on ulcerative colitis'
Michelle Linterman (University of Cambridge, UK)	'Endurance of established germinal centers in absence of T cell help'
Yueh-Hsiu Chien (Stanford University, USA)	'Gamma Delta T cell antigen receptor poly-specificity enables T cell response to a broad range of immune'
Saya Moriyama (National Institute of Infectious Diseases, Japan)	'Neutralizing antibodies against SARS-CoV-2 variants'
James B. Wing (CiDER/IFReC, Osaka University)	'Atypical and non-classical CD45RBlo memory B cells are the majority of circulating SARS-CoV-2 specific B cells following mRNA vaccination'
Mark M. Davis (Stanford University, USA)	'Immune organoids and combinations to advance our understanding of autoimmunity, vaccination and infection'


International Symposium
on Microbiology and Immunology
The 14th International Symposium of IFReC
November 12 (Tue) 2024

The Third University College London - Osaka University Joint Symposium on Immunology

Date: September 26, 2024

Venue : Taniguchi Memorial Hall, Osaka University

Speakers (order of presentation)	Title
Tadamitsu Kishimoto (IFReC, Osaka University)	'Interleukin6; from its discovery to clinical application Past, Present and Future'
Kiyoshi Takeda (IFReC, Osaka University)	'Host-microbiota interaction for intestinal homeostasis'
Jennifer Cowan (UCL)	'Reversal of Thymic Involution Delays Age-Associated Mortality of Toxoplasma gondii Challenged Mice'
Laura Pallett (UCL)	'Tissue CD14+CD8+ T cells reprogrammed by myeloid cells and modulated by LPS'
Hisashi Arase (IFReC, Osaka University)	'The Crucial Role of Self and Neoself Discrimination by T cells in the Pathogenesis of Autoimmune Diseases'
Daron Standley (IFReC, Osaka University)	'Robust detection of infectious disease, autoimmunity, and cancer from the paratope networks of adaptive immune receptors'
James Wing (IFReC, Osaka University)	'Atypical and non-classical CD45RBlo memory B cells are the majority of circulating SARS-CoV-2 specific B cells following mRNA vaccination or COVID-19'
Shimon Sakaguchi (IFReC, Osaka University)	'Treatment of autoimmune disease by converting disease-mediating T cells into Treg cells'
Masahiro Yamamoto (IFReC, Osaka University)	'Mechanism of Th1-Treg induction in tumor'
Anne Pesenacker (UCL)	'Immunoregulation in childhood arthritis: from Treg signatures to co-receptors'
David Sansom (UCL)	'Understanding the impact of CD80 and CD86 on CTLA-4 and PD-1 function'
Benedict Seddon (UCL)	'A linear ontogeny accounts for the development of naive, memory and tumour-infiltrating regulatory T cells in mice'
Pavel Tolar (UCL)	'Mutations in the IgG B cell receptor associated with class-switched B cell lymphomas'
Lucy Walker (UCL)	'Regulation of T cell costimulation by CTLA-4-dependent ligand regulation'
Sho Yamasaki (IFReC, Osaka University)	'Deciphering clonotypic responses of human T cells'

IFReC Seminar Series

- A wide variety of scientists has been invited as speakers.
- Each seminar is a credit seminar for the Graduate School of Medicine and the Graduate School of Frontier Biosciences.

Date	Speaker
May 3, 2024	**Stephen Kent** (Professor, Microbiology and Immunology, Peter Doherty Institute, University of Melbourne, Australia)
May 27, 2024	**Di Yu** (Chair in Paediatric Immunotherapy, Child Health Research Centre, Faculty of Medicine, The University of Queensland, Australia)
July 2, 2024	**Michael Otto** (Chief, Pathogen Molecular Genetics Section, National Institute of Allergy and Infectious Diseases, USA)
July 29, 2024	**Dylan Dodd** (Assistant Professor, Pathology and of Microbiology & Immunology, Stanford University School of Medicine, USA)
August 19, 2024	**Hans Stauss** (Professor, Tumour Immunology/Director, UCL Institute of Immunity & Transplantation, UK)
October 9, 2024	**Kazuki Nagashima** (Assistant Professor in the Department of Molecular and Cellular Biology at Harvard University, USA)
October 23, 2024	**Hiroki Ueda** (Professor, Graduate School of Medicine, University of Tokyo/Team Leader, RIKEN BDR)
November 5, 2024	**Makoto Miyara** (Professor, Department of Immunology, Pitie-Salpetriere Hospital, AP-HP, University of Sorbonne, Paris, France)
November 27, 2024	**Andreas Diefenbach** (Director, the Institute of Microbiology and Infection Immunology / Charité - University Medicine Berlin, Germany)
November 28, 2024	**Tim Sparwasser** (Professor, Institute of Medical Microbiology and Hygiene, University Medical Center of the Johannes Gutenberg-University Mainz, Germany)
December 6, 2024	**Cherilyn Sirois** (Scientific Editor at the journal Cell, Cell Press, Cambridge, USA)
December 12, 2024	**Takeshi Egawa** (Professor, Pathology & Immunology, Washington University School of Medicine, St. Louis, USA)
March 24, 2025	**Branch Moody** (Professor, Division of Medical Sciences, Harvard Medical School/Brigham and Women's Hospital, USA)
March 28, 2025	**Caleb Lareau** (Principal Investigator, Computational and Systems Biology Program, Memorial Sloan Kettering Cancer Center, USA)

Technical Seminars

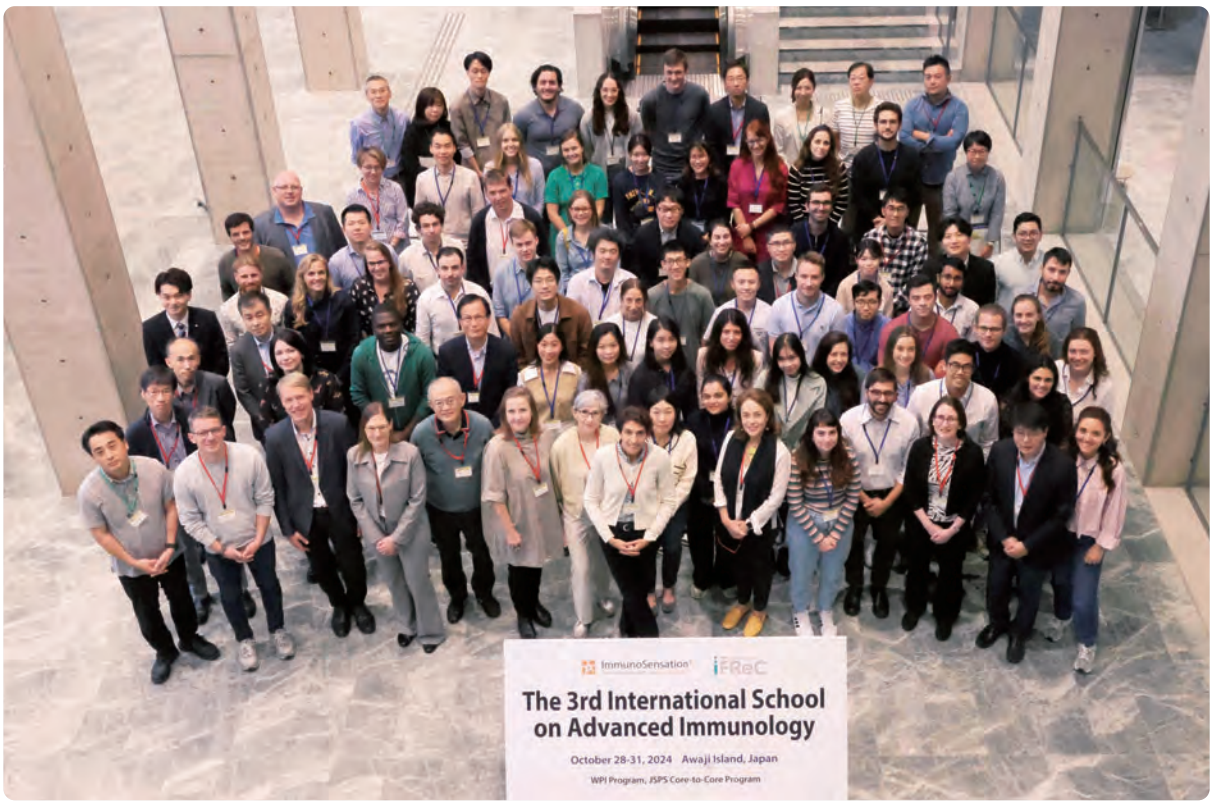
Date	Contents	Presenter
June 20, 2024	Seahorse XF technologies	**Yuki Ueda** (Primetech Co.)
July 25, 2024	Single-cell & spatial transcriptomics data analysis	**Jenny Pham** (Pythia Biosciences)
Sep. 25, 2024	Single-cell & spatial transcriptomics data analysis	**Jenny Pham** (Pythia Biosciences)
Sep. 4, 2024	Organoid culture and co-culture of immune cells	**Daisuke Sakano** (STEMCELL Technologies Inc.)
Oct. 15, 2024	Cell isolation and culture techniques in immunology research	**Jun-ichi Hitomi** (STEMCELL Technologies Inc.)

The Third ImmunoSensation² - IFReC International School on Advanced Immunology

The Third International School on Advanced Immunology was held in Awaji island. Fifteen leading immunologists were invited as lecturers, and 50 exceptional participants were selected from 336 applicants. The cutting-edge research presented by the participants and the active exchanges that promoted interaction among them were highly praised by both lecturers and participants.

- **Date:** October 28-31, 2024
- **Venue :** The Awaji Yumebutai International Conference Center, Hyogo, Japan

Lecturers
Hisashi Arase (IFReC, Osaka University, Japan)
Sidonia Fagarasan (RIKEN-IMS, Japan)
Gunther Hartmann (ImmunoSensation², University of Bonn, Germany)
Jan Hasenauer (ImmunoSensation², University of Bonn, Germany)
Claudia Kemper (NIH, USA)
Taku Okazaki (The University of Tokyo, Japan)
Katrin Paeschke (ImmunoSensation², University of Bonn, Germany)
Andreas Schlitzer (ImmunoSensation², University of Bonn, Germany)
Maria Rescigno (Humanitas University, Italy)
Feng Shao (National Institute of Biological Sciences, China)
Kazuhiro Suzuki (IFReC, Osaka University, Japan)
Gabriel Victora (The Rockefeller University, USA)
Carola G. Vinuesa (Francis Crick Institute, UK)
Lucy Walker (University College London, UK)
Dietmar Zehn (Technical University of Munich, Germany)

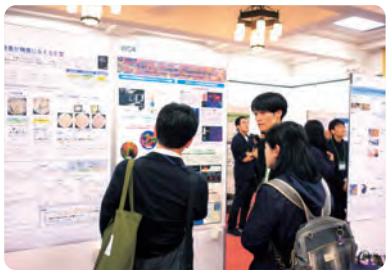

ImmunoSensation
iFReC
The 3rd International School
on Advanced Immunology
October 28-31, 2024 Awaji Island, Japan
WPI Program, JSPS Core-to-Core Program

Outreach Activities

In 2024, we have organized various outreach events. An interaction with the general public is a good stimulus for researchers. We think an approaching to high school students and high school teachers is especially important for the future development of science and technology.

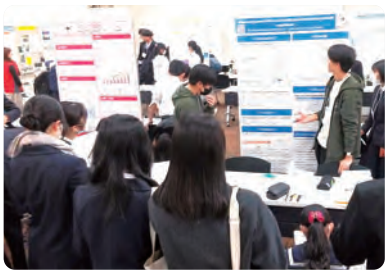
The 13th WPI Science Symposium "The world unfolds through science"

- Date : November 16, 2024
- Venue : The Clock Tower Centennial Hall at Kyoto University
- Organizers : WPI-ASHBi and WPI institutions.



Exploring Research at WPI : Guide for students and educators

- July 13, 2024@Meijo University, Nagoya
- July 23, 2024@online
- December 25, 2024@Okazaki Conference Hall, Aichi



Life Science Seminar for high school students

- Date : August 6, 2024
- Venue : Taniguchi Memorial Hall, RIMD and IFReC
- Speakers : Ai Kotani (RIMD, Osaka University) and Kazutaka Miyazawa (Graduate School of Engineering Science, Osaka University)

Science Café at the Nakanoshima Festival “Organoids pioneer the future of medicine”

- Date : December 1, 2024
- Venue : Lecture Hall A, Osaka University School of Medicine
- Speaker : Masashi Okamoto (WPI-PRIMe/Graduate School of Medicine, Osaka University)

Contribution to “Team Handai” project

In July 2020, Osaka University launched the "Team Handai Project" to promote research and development on COVID-19 across fields and organizations. The core of the project was comprised of members from IFReC. Although "Team Handai" was dissolved in March 2025, it had been publishing booklets introducing Osaka University's research on infectious diseases to the general public until then.

Japanese Language Class

The Japanese language classes hosted by IFReC focus on speaking practice. Students are encouraged to use the grammar and vocabulary learned in class to talk about themselves. Additionally, we hold parties a few times a year to foster friendships among students. Ms. Kaori Tajima, our experienced Japanese teacher, is looking forward to meeting you all.

Message from an instructor

Hi. I'm Kaori Tajima. It's been really enjoyable to teach Japanese at IFReC and I'm always excited to meet new members in April. The class is focused on speaking, so you are expected to talk about various things like your hobbies, weekends, experiences in Japan, and so on. I hope you enjoy learning Japanese grammar and vocabulary as well as communicating with your classmates!


Information

Major Awards

Highly Cited Researchers (HCR) 2024 by Clarivate™

Nobuhiko Kamada

Shimon Sakaguchi

The Garnet Immunoglobulin by the Czech Immunological Society 2024

Shimon Sakaguchi

The Takamine Memorial Daiichi Sankyo Award 2024

Kiyoshi Takeda

The Japanese Society for Immunology (JSI) Award 2024

Kazuhiro Suzuki

Osaka University Prize 2024

Taiichiro Shirai

RIKEN EIHO Award

Yukinori Okada

The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (Research Category)

Masaru Ishii

Advanced Postdoc Program at IFReC

IFReC has been recruiting postdoctoral researchers for its Advanced Postdoc Program. This program offers three-year employment and funding (3 million JPY per year) for original research to promising young researchers. Selected applicants have access to continually upgraded state-of-the-art facilities at IFReC for their research, including equipment for single-cell analysis.

Support for Paper Submission

This program aims to support the dissemination of research results by young researchers of IFReC.

IIT-IFReC Exchange Program for Young Researchers

This program started in 2024, and promises IFReC supports selected young researchers a one-month visit to the Institute of Immunology and Transplantation (IIT) at the University College London, UK.

Original Support Programs for Young Researchers

To strengthen our international research network and our basis for international collaborative research, IFReC has established two kinds of financial support programs for researchers.

1) "IFReC Kishimoto Foundation Fellowship," which has been used to invite international researchers to Osaka.

2) "Program for International Circulation of Young Talented Researchers" for those who wish to participate in overseas research activities. Since 2009, about 150 researchers have received these grants.

Common Facilities (IFReC, RIMD, Animal Resource Center)

IFReC and its parent institution, the Research Institute for Microbial Diseases (RIMD) are located on the same site, constituting a large research complex. The complex contains the Core Instrumentation Facility, the Animal Resource Center and the Network Administration Office, all of which are jointly operated by IFReC and RIMD. The Core Instrumentation Facility is equipped with various highly advanced instruments and skilled technicians provide in-house services to IFReC and RIMD researchers. The Animal Resource Center consists of three buildings for specific pathogen-free (SPF) animals and the live immuno-imaging facility. With a largecapacity animal-breeding facility in IFReC, researchers are able to choose animal rooms suitable for their experiment purpose. Using these common facilities, IFReC researchers are able to effectively and smoothly carry out their experiments to promote their world-leading research at IFReC.

1. **IFReC Research Building**
2. **Integrated Life Science Building**
3. **Main Building, Research Institute for Microbial Diseases, RIMD**
4. **South Building, Research Institute for Microbial Diseases, RIMD**
5. **Cutting-Edge Research Building for Infectious Diseases**
6. **Animal Resource Center for Infectious Diseases**

Animal Resource Center for Infectious Diseases

- Specific pathogen-free (SPF) animal facility
- Sperm/ embryo freezing and preservation
- In vitro fertilization and embryo transplantation
- Intracytoplasmic sperm injection
- Transgenic and knock-out animals
- Genome editing in experimental animals

Live immuno-imaging facility

- SPF animal experiment facility with 11.7T MRI, in vivo imager & two-photon microscope.

Network Administration Office

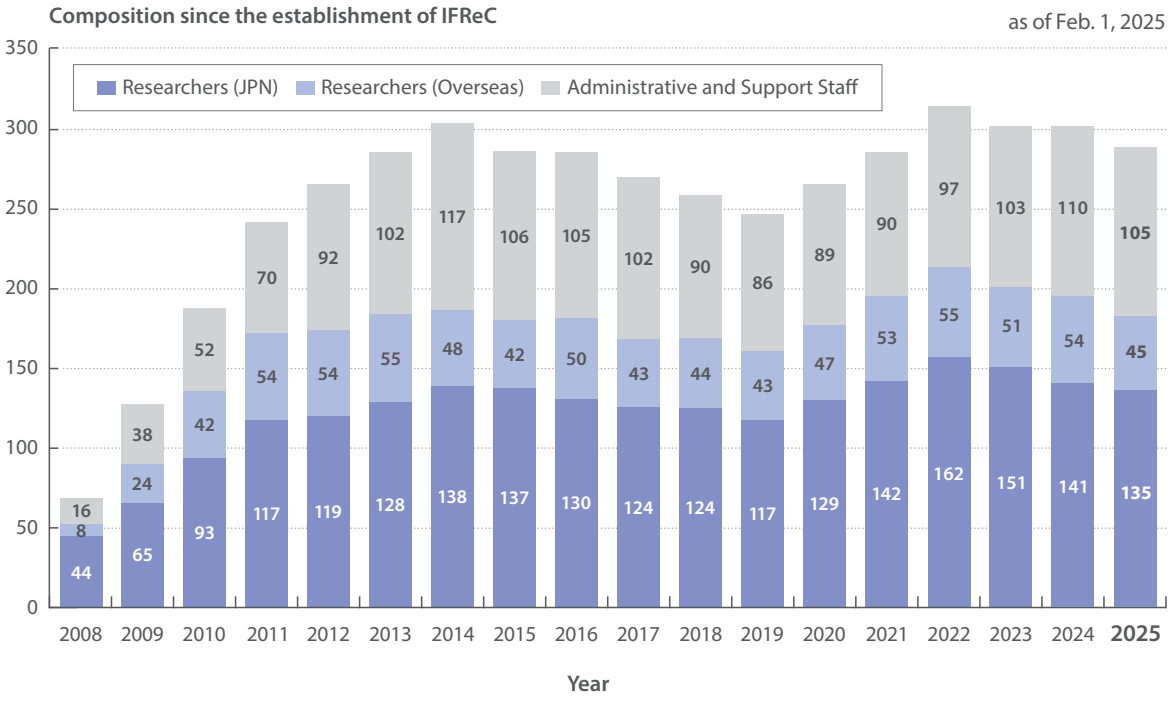
- Provision and maintenance of network infrastructure: LAN system and servers (web, mail, mailing lists, etc.)

Core Instrumentation Facility

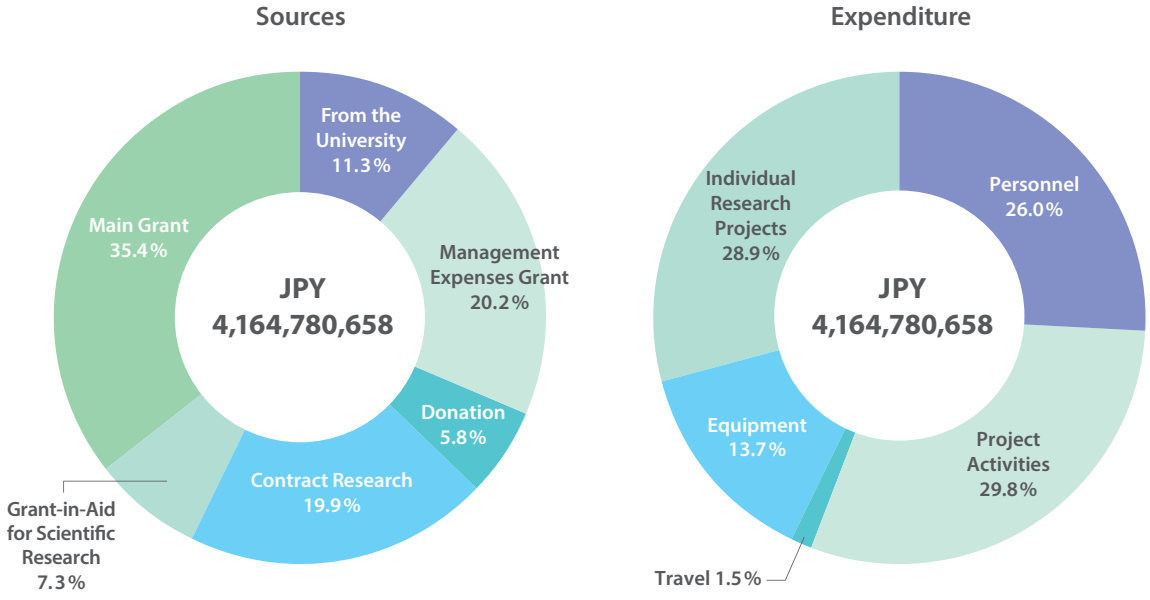
- Basic and advanced instruments
- In-house service
- DNA sequencing, cell sorting, electron microscopy, mass spectrometry and next-generation sequencing analysis
- Radio isotope facility

Composition & Finance

Composition



Finance



Selected Articles

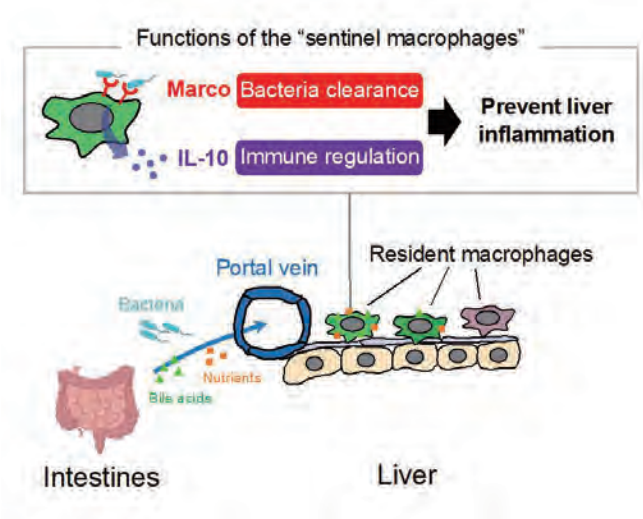
Periportal macrophages protect against commensal-driven liver inflammation.

Miyamoto Y, Kikuta J, Matsui T, Hasegawa T, et al.

Nature 629 : 901-909 (2024).

DOI : 10.1038/s41586-024-07372-6

The intestines harbor numerous gut bacteria, and these bacteria, along with their associated substances, often enter the liver via the portal vein. Particularly in conditions where the barrier function of the intestines is compromised, such as ulcerative colitis or leaky gut syndrome, many gut bacteria and associated substances can easily enter the liver, leading to inflammation in the liver. Yu Miyamoto, Masaru Ishii and the research group revealed the periportal localization of a resident macrophage subtype highly expressing the scavenger receptor, Marco, and the anti-inflammatory protein, interleukin-10.



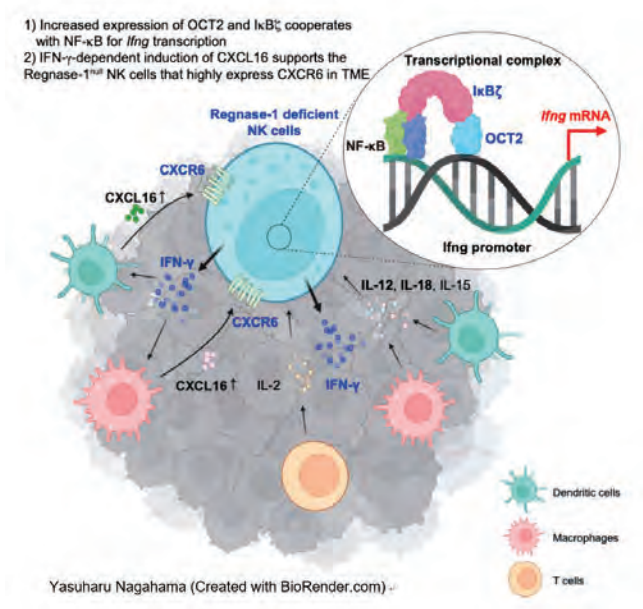
Deletion of Regnase-1 promotes NK cell anti-tumor activity.

Sun X, Nagahama Y, et al.

Immunity 57 : 1360-137.e13 (2024).

DOI : 10.1016/j.immuni.2024.05.006

Natural killer (NK) cells play a crucial role in the first line of host defense by eliminating bacteria, viruses, and mutated cells that might become cancer cells. Xin Sun, Diego Diez, Yasuharu Nagahama and Shizuo Akira revealed that deletion of mRNA endonuclease Regnase-1 promoted NK cell anti-tumor activity via OCT2-dependent transcriptional up-regulation of IFNγ mRNA.



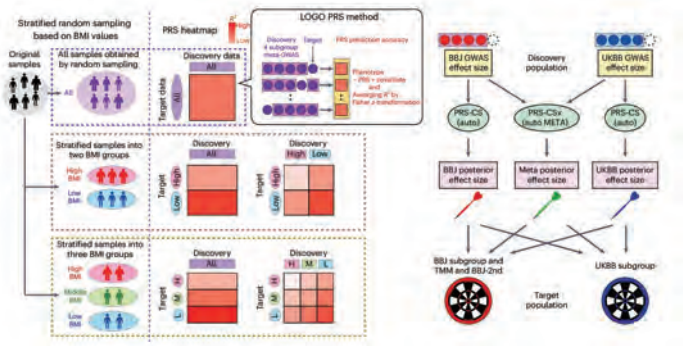
Body mass index stratification optimizes polygenic prediction of type 2 diabetes in cross-biobank analyses.

Ojima T, Namba S, Suzuki K, et al.

Nature Genetics 56 : 1100-1109 (2024).

DOI : 10.1038/s41588-024-01782-y

The scarcity of genome data from Japanese may potentially lead to reduced accuracy in predicting the risk of type 2 diabetes and could contribute to a decline in the future of genomic medicine in Japan. Despite the limited data, the research group led by Yukinori Okada succeeded in improving the predictive accuracy by incorporating body mass index (BMI) into the genomic information. Their approach improves the ability to determine whether an individual is likely to develop type 2 diabetes.



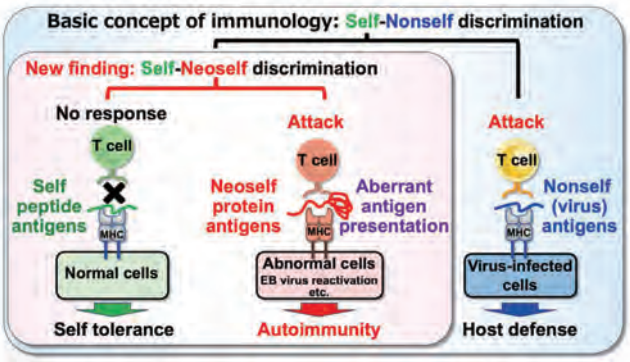
Neoself-antigens are the primary target for autoreactive T cells in human lupus.

Mori S, Kohyama M, Yasumizu Y, et al.

Cell 187 : 6071-6087.e20 (2024).

DOI : 10.1016/j.cell.2024.08.025

It has been a mystery why immune cells that eliminate viruses and other pathogens attack the own tissues and cells in autoimmune diseases. The research group of Hisashi Arase revealed that autoimmune diseases are caused when T cells recognize abnormal self-antigens called "neoself "as non-self and attack the own tissues. This result significantly changes the basic concepts of conventional immunology and is an important discovery for developing new treatments of autoimmune diseases and for understanding pathological immune responses.



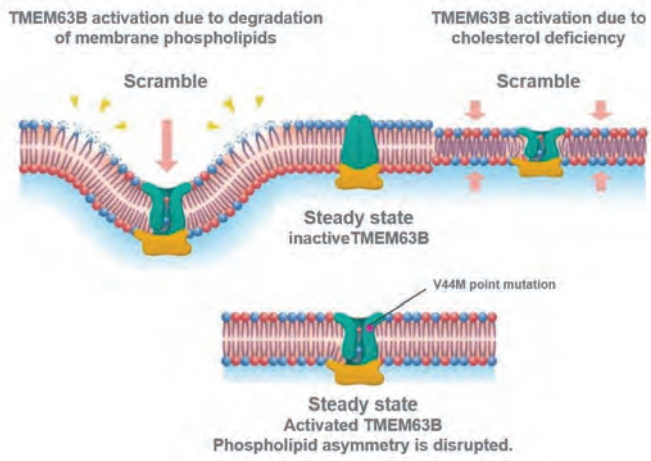
Membrane structure-responsive lipid scrambling by TMEM63B to control plasma membrane lipid distribution.

Miyata Y, Takahashi K, et al.

Nature Structural & Molecular Biology
32:185-198 (2025).

DOI : 10.1038/s41594-024-01411-6

In animal cells, the plasma membrane (PM) exhibits an asymmetrical distribution of phospholipids. Although phosphatidylcholine (PC) and sphingomyelin (SM) are the most abundant phospholipids in the PM and have documented roles in human diseases, the mechanisms regulating their distribution remain unclear. The research group led by Katsumori Segawa and Shigekazu Nagata found that TMEM63B functions as a lipid scramblase at the PM and at lysosomal membranes, mediating bidirectional scrambling of various phospholipids in response to changes in membrane structure, such as membrane thickness (induced by cholesterol depletion) and membrane curvature (induced by phospholipase treatment).



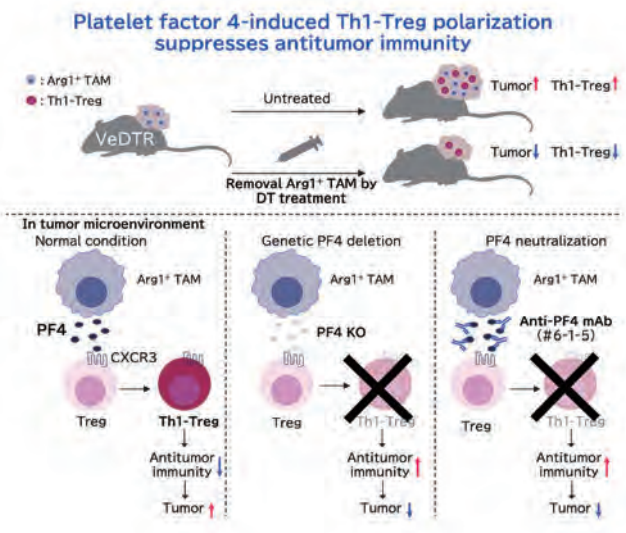
Platelet factor 4-induced TH1-Treg polarization suppresses antitumor immunity.

Ayumi Kuratani, Masaaki Okamoto, Kazuki Kishida, et al.

Science 386:6724 (2024).

DOI : 10.1126/science.adn8608

It has been known that Th1-Tregs, a subset of Tregs that strongly suppress cancer immunity in tumors, highly accumulate in tumors, but the molecular mechanism of this accumulation was unclear. The research group of Masahiro Yamamoto revealed that the chemokine PF4 produced by macrophages (Arg1+TAM) that produce arginase 1 (Arg1) in tumors induces Th1-Treg and suppresses cancer immunity. It is highly anticipated that PF4 becomes a new target for cancer immunotherapy in the future.



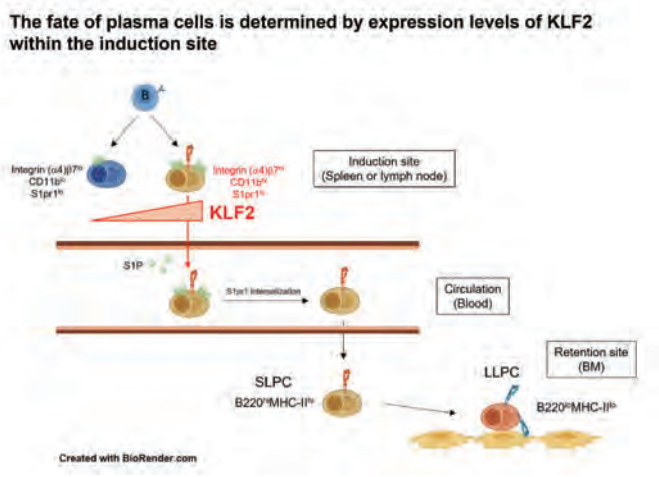
KLF2 expression in IgG plasma cells regulates the migration program.

Wataru I, Koike T, et al.

Journal of Experimental Medicine
222: e20241019 (2025).

DOI : org/10.1084/jem.20241019

Antibody-producing cells (plasma cells) can be found in a variety of tissues across the body that can be divided into two sites--where they differentiate from activated B cells (induction site) and the tissues where they migrate to robustly secrete their antibodies (effector tissues). However, the question of what the key determinant(s) for plasma cell longevity are has remained unanswered. The research group of Wataru Ise and Tomohiro Kurosaki (RIKEN/IFReC/CiDER) discovered cells that migrate from plasma cells born in lymphoid tissues to the bone marrow, which is their long-term survival site.



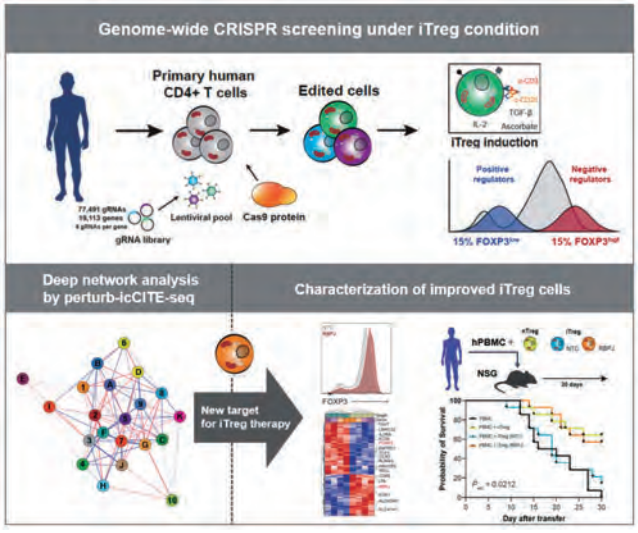
Genome-wide CRISPR screen in human T cells reveals regulators of FOXP3.

Chen KY, Kibayashi T, et al.

Nature (2025).

DOI : 10.1038/s41586-025-08795-5

While stimulation of naive CD4+ T cells in the presence of TGF-β and IL-2 can induce FoxP3+ Tregs in vitro (iTregs), the resulting cells are often unstable and have thus far hampered translational efforts in cell therapies for autoimmune diseases. Shimon Sakaguchi and Innovative Drug Discovery group performed a genome-wide CRISPR loss-of-function screen to catalog gene regulatory determinants of FOXP3 induction in primary human T cells. They identified the RBPJ-NCoR repressor complex as a novel, context-specific negative regulator of FOXP3 expression.



Publications

1. Abe K, Eki H, Hirose Y, Park S, Chinnathambi S, Namasivayam GP, Takeda K, Sugiyama H, Endo M. Creation of Metal-Complex-Integrated Tensegrity Triangle DNA Crystals. Molecules 29, 4674 (2024).
2. Abe K, Ino H, Niwa T, Semmy D, Takaochi A, Nishimura T, Mogi C, Uenaka M, Ishii M, Tanaka K, Ohkawa Y, Ishitani T. Sex-dependent regulation of vertebrate somatic growth and aging by germ cells. Science Advances 10, eadi1621 (2024).
3. Adachi Y, Miyake K, Ohira K, Satoh S, Masuhiro K, Edahiro R, Shirai Y, Naito M, Naito Y, Shiroyama T, Koyama S, Hirata H, Iwahori K, Nagatomo I, Takeda Y, Kumanogoh A. Enhancing the efficacy of near-infrared photoimmunotherapy through intratumoural delivery of CD44-targeting antibody- photoabsorber conjugates. Ebiomedicine 112, 105566 (2025).
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The articles were published between April, 2024 and March, 2025. The data was acquired using Web of ScienceTM Core Collection on May 10, 2025, and sorted by alphabetical order of the first authors.

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Edit : Research Planning & Management Office, IFReC
Published in June, 2025