The University of Osaka

Immunology Frontier Research Center

Annual Report of IFReC 2025-2026

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 2025. Since joining the WPI Academy in 2017, we at IFReC have pioneered a unique academic-industry partnership that unleashes new possibilities in collaborative research.

In 2025, we at IFReC received remarkable news. Professor Shimon Sakaguchi, a central Principal Investigator at IFReC, was awarded the Nobel Prize in Physiology or Medicine. The regulatory T cells discovered by Professor Sakaguchi have been pivotal in elucidating immune tolerance and have also demonstrated great potential for broad applications in immunotherapy, with far-reaching benefits for humanity. This achievement exemplifies the path that IFReC should continue to pursue in the future.

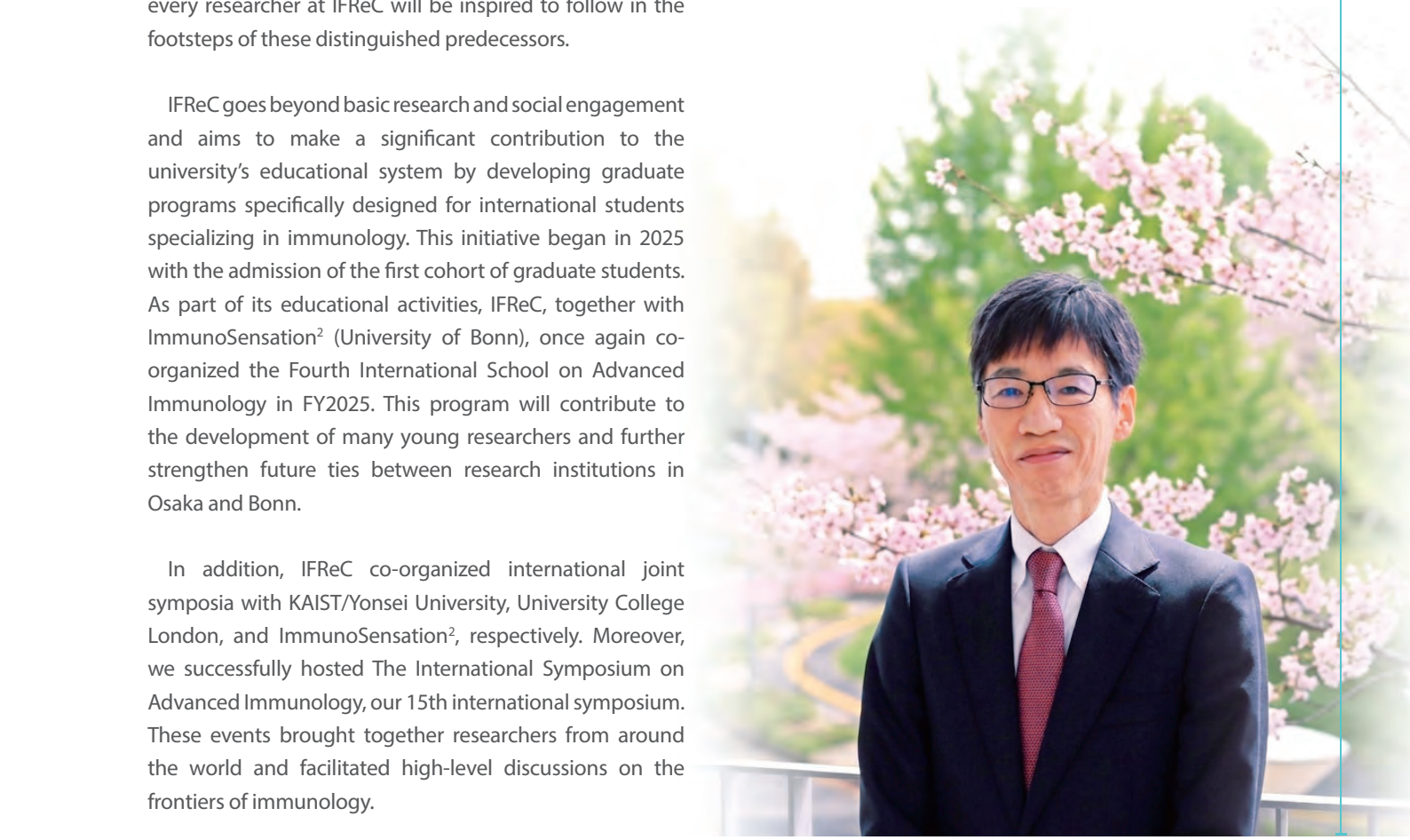
In 2026, Professor Shizuo Akira, the founding director of IFReC, was awarded the Japan Prize. This prestigious award, often referred to as the "Japanese Nobel Prize," recognizes the significance of Professor Akira's elucidation of pathogen recognition by the innate immune system. I hope that every researcher at IFReC will be inspired to follow in the footsteps of these distinguished predecessors.

IFReC goes beyond basic research and social engagement and aims to make a significant contribution to the university's educational system by developing graduate programs specifically designed for international students specializing in immunology. This initiative began in 2025 with the admission of the first cohort of graduate students. As part of its educational activities, IFReC, together with ImmunoSensation^2 (University of Bonn), once again co-organized the Fourth International School on Advanced Immunology in FY2025. This program will contribute to the development of many young researchers and further strengthen future ties between research institutions in Osaka and Bonn.

In addition, IFReC co-organized international joint symposia with KAIST/Yonsei University, University College London, and ImmunoSensation^2, respectively. Moreover, we successfully hosted The International Symposium on Advanced Immunology, our 15th international symposium. These events brought together researchers from around the world and facilitated high-level discussions on the frontiers of immunology.

IFReC plays a central role in immunology and infectious disease research by fostering collaborations among multiple research departments and institutes, including 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 remain committed to advancing basic research in immunology and to exploring ways to make meaningful contributions to society. Through both research and education, IFReC will continue to drive scientific progress and help shape the future of immunology research worldwide.

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

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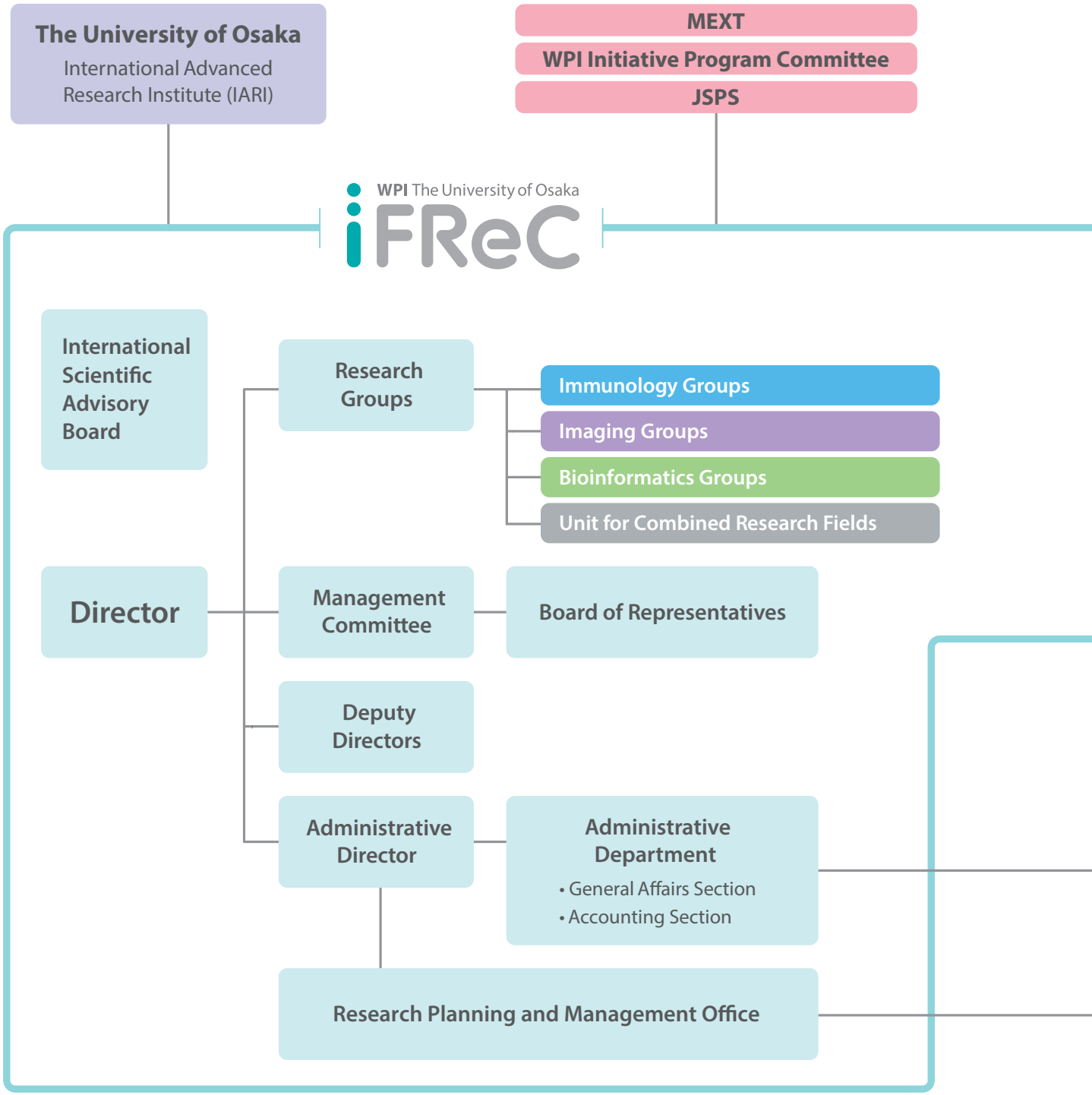
Organization

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[3], 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, South Korea

As of April 2026

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 (International 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, 2025

Akira UKAWA	WPI Program Director and Academy Director

Program Committee Members

Michinari HAMAGUCHI (Chairperson)	Director General, Strategic Center of 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)
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Ryozo NAGAI	President, Jichi Medical University, Japan
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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), Singapore
Mona NEMER	Chief Science Advisor, Government of Canada, Canada
Jean ZINN-JUSTIN	Visitor , Institute of Theoretical Physics, Alternative Energies and Atomic Energy Commission (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, 2026

Anne O'GARRA	The Francis Crick Institute, UK
Mark M. DAVIS	Stanford University, USA
Andreas DIEFENBACH	Charité - University Medical Center Berlin, Germany
Carla ROTHLIN	University of Minnesota, USA
Kayo INABA	Kyoto University, Japan
Hiroshi KIYONO	Future Medicine Education and Research Organization, Chiba University, Japan
Kazuhiko YAMAMOTO	RIKEN Center for Integrative Medical Sciences (RIKEN IMS), Japan
Osamu OHARA	Kazusa DNA Research Institute, Japan
Kenta NAKAI	The Institute of Medical Science, The University of Tokyo (IMSUT), Japan

In Honor of Dr. Shimon Sakaguchi

The Nobel Prize Committee has announced that the 2025 Nobel Prize in Physiology or Medicine will be awarded to Dr. Shimon Sakaguchi of The University of Osaka, together with two other scientists. The prize motivation is "for their discoveries concerning peripheral immune tolerance".

The immune system, while essential for protecting the body, must be precisely regulated; otherwise, it may turn against the body's own tissues, giving rise to autoimmune disease. By 1995, Dr. Sakaguchi demonstrated that the selective removal of approximately 10 percent of CD4 T cells expressing the CD25 protein induced severe autoimmune symptoms in mice. Remarkably, reinfusion of this same cell population led to complete resolution of the disease. Through these experiments, Dr. Sakaguchi identified a distinct population of suppressive T cells, which he named regulatory T cells, or Tregs.

Following the landmark discovery by Mary Brunkow and Fred Ramsdell that mutations in a single gene can cause fatal autoimmune disease, Dr. Sakaguchi subsequently demonstrated that this gene governs the development and function of the regulatory T cells he had identified, thereby establishing a direct genetic basis for immune tolerance.

Dr. Sakaguchi's work fundamentally transformed the field of immunology. By revealing immune regulation as an active, cell-mediated process, his discoveries provided critical insight into the mechanisms of autoimmunity and opened entirely new avenues for therapeutic intervention in autoimmune diseases, transplantation, and cancer immunotherapy.

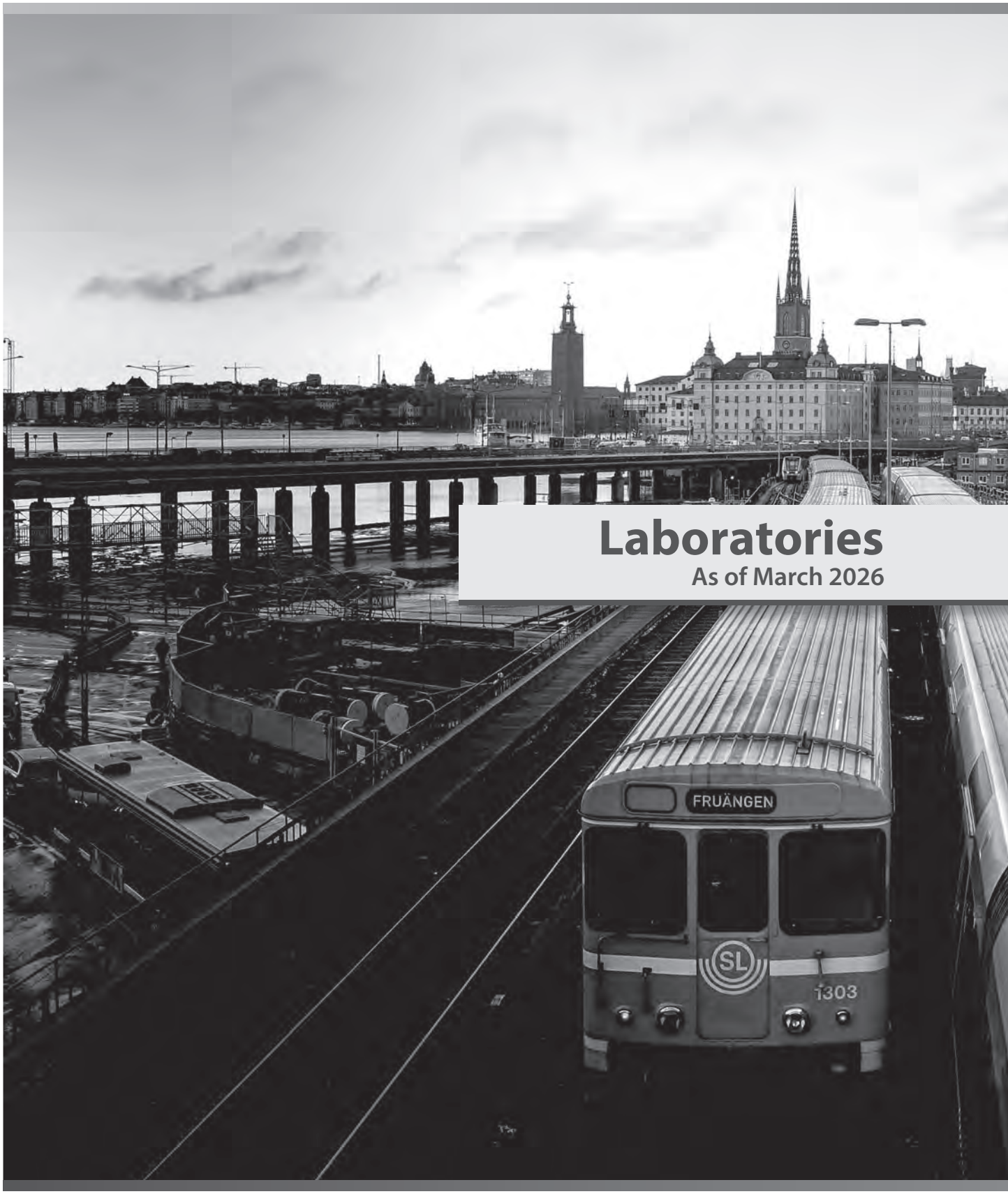
At a press conference held immediately after the announcement, Dr. Sakaguchi remarked, "There were certainly times when my research was not fully recognized. Nevertheless, I trusted my experimental findings and continued step by step. I am deeply grateful to my wife, my collaborators, and all those who supported me along the way."

During the award ceremony and Nobel Week in Sweden in December 2025, Dr. Sakaguchi participated in numerous academic and public events, addressing audiences across generations on the promise of immune regulation and its clinical applications. Following his return to Japan, he has continued his vigorous scientific and educational activities.

In recognition of this historic achievement, The University of Osaka conferred upon Dr. Sakaguchi the title of Distinguished Honorary Professor.

Dr. Sakaguchi at the press conference on October 6, 2025.
Photo: The University of Osaka

Dr. Sakaguchi receiving his Nobel Prize from H.M. King Carl XVI Gustaf of Sweden at Konserthuset Stockholm on December 10, 2025.
© Nobel Prize Outreach. Photo: Nanaka Adachi



Laboratories

As of March 2026

Host Defense

Shizuo Akira, MD/PhD

▶ Professor	Shizuo Akira
▶ Associate Professor	Kazuhiko Maeda
▶ Assistant Professor	Akihiko Murata
▶ Research Assistant	1
▶ Visiting Scientist	3
▶ Support Staff	2

Our research aims to elucidate host defense mechanisms against pathogens by integrating both innate and adaptive immune perspectives, thereby contributing to the development of novel therapeutic strategies for immune-related diseases. Central to this effort is the RNA-binding protein Regnase-1, a key regulator of immune homeostasis that modulates inflammatory responses through the selective degradation of target RNAs. In this year's work, we explored its function in natural killer (NK) cells, assessed the impact of its RNase activity using nuclease-deficient mutants, and initiated studies toward understanding its role in metabolic dysfunction-associated steatohepatitis (MASH) resistance using a hepatocyte-specific *Regnase-1*-deficient animal model.

Role of Regnase-1 in NK Cells

In our study, we demonstrated that Regnase-1 functions as a critical negative regulator of NK cell–mediated antitumor immunity. Using NK cell–specific *Regnase-1*–deficient mice (Regnase-1$^{\Delta NK}$), we found markedly enhanced NK cell effector functions, including increased IFN-γ production and elevated cytolytic protein expression.

Both splenic and tumor-infiltrating NK cells exhibited an activated phenotype with upregulated cytotoxic gene programs. Notably, *Regnase-1* deficiency led to increased expression of CXCR6, promoting NK cell infiltration into tumors in an IFN-γ–dependent manner, partly through induction of CXCL16 in the tumor microenvironment.

Mechanistically, we showed that the transcription factors OCT2 and IκBζ were upregulated and cooperated with NF-κB to enhance *Ifng* transcription. Collectively, our findings establish Regnase-1 as a molecular brake on NK cell activation and tumor trafficking and suggest that its inhibition could potentiate NK cell–based immunotherapies.

Role of Nuclease-Null Regnase-1 in Immune Regulation

We investigated the functional importance of Regnase-1 RNase activity using a catalytic mutant (D141N) lacking endonuclease activity. These mice developed systemic inflammation, characterized by extensive immune cell infiltration and granuloma formation, particularly in the lungs.

We found that CD4$^+$ T cells exhibited hyperactivation of the mTORC1 pathway and autoimmune-like features. RNA-seq analysis identified the serine/threonine kinase Pim2 as a key upregulated target. Importantly, Pim2 inhibition significantly reduced granulomatous inflammation, immune cell infiltration, and adhesion molecule expression on CD4$^+$ T cells, indicating impaired migration into inflamed tissues.

Mechanistically, our data demonstrate that *Pim2* is a direct target of Regnase-1, linking defective RNA degradation to enhanced immune cell adhesion and trafficking. Collectively, these findings establish that the RNase activity of Regnase-1 is essential for preventing immune dysregulation and highlight Pim2 as a potential therapeutic target in inflammatory diseases.

Role of Regnase-1 in MASH development

These findings suggest that Regnase-1 may also promote inflammatory and metabolic processes in non-immune tissues. However, its role in MASH has remained unclear. To address this, we investigated the impact of hepatocyte-specific *Regnase-1* deficiency on MASH progression. Using an AAV-TBG-Cre system in *Regnase-1*$^{flox/flox}$ mice subjected to a MASH-inducing diet, we found that loss of *Regnase-1* in hepatocytes markedly attenuated both

hepatic steatosis and fibrosis, even under continued dietary stress. Mechanistically, transcriptomic and metabolic analyses revealed enhanced mitochondrial spare respiratory capacity and increased reduced glutathione levels, accompanied by normalization of mitochondrial morphology. Importantly, therapeutic silencing of *Regnase-1* using GalNAc-conjugated siRNA recapitulated these protective effects. Collectively, these findings identify hepatocyte Regnase-1 as a key driver of MASH progression through modulation of mitochondrial metabolism and highlight its inhibition as a promising therapeutic strategy.

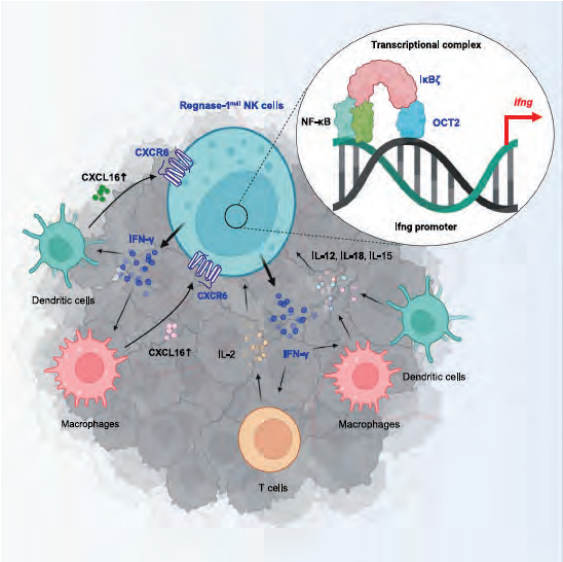


Figure 1.
Low persistence and reduced activity of NK cells limit antitumor immunity. NK cell-specific deficiency of the endonuclease Regnase-1 promotes NK cell persistence in the tumor microenvironment via sustained CXCR6 expression and enhances antitumor activity through increased *Ifng* transcription mediated by OCT2.

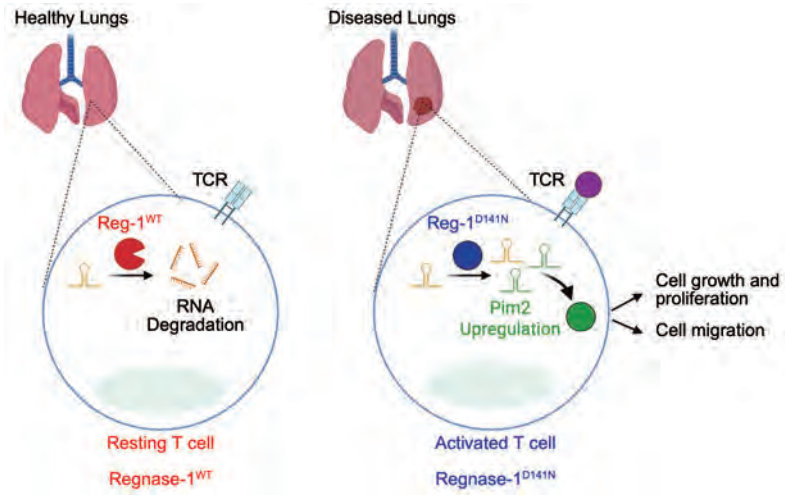


Figure 2.
Regnase-1 RNase activity maintains immune homeostasis by degrading target mRNAs such as Pim2, thereby limiting TCR signaling, mTORC1 activation, and CD4⁺ T cell activation in the steady-state lung. Loss of Regnase-1 RNase activity (D141N mutation) leads to Pim2 upregulation, enhanced mTORC1 signaling, and increased adhesion molecule expression, promoting CD4⁺ T cell infiltration and granulomatous inflammation in the lung.

Recent Publications

1. Sakaguchi T, Nagahama Y, Hamada N, Singh SK, Mikami H, Maeda K, Akira S. 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 in male mice. Nutrients 16, 4151 (2024).

2. 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 (2024).

3. Kawai T, Ikegawa M, Ori D, Akira S. Decoding Toll-like receptors: Recent insights and perspectives in innate immunity. Immunity 57, 649–673 (2024).

4. Htun TS, Tanaka H, Singh SK, Diaz D, Akira S. Regnase-1 D141N mutation induces CD4⁺ T cell-mediated lung granuloma formation via upregulation of Pim2. International Immunology 36(10), 497–516 (2024).

5. Akira S, Maeda K. Control of RNA stability in immunity. Annual Review of Immunology 39, 481–509 (2021).

Immunochemistry

Hisashi Arase, MD/PhD

▶ Professor	Hisashi Arase
▶ Associate Professor	Hui Jin
▶ Assistant Professor	Shunsuke Mori
▶ Postdoctoral Fellow	2
▶ Research Assistant	5
▶ 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.

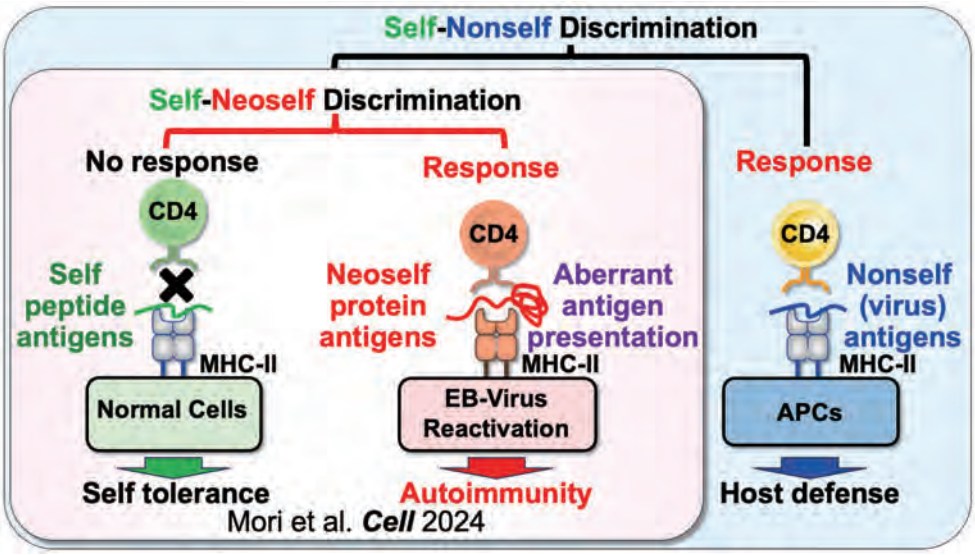


Figure 1.
Self and Neoself Discrimination by T Cells in the Pathogenicity of Autoimmune Diseases.
Self-antigens can be subdivided into self-peptide antigens—normally presented on MHC class II molecules—and neoself antigens, which are aberrantly presented on these molecules. T cells are capable of distinguishing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

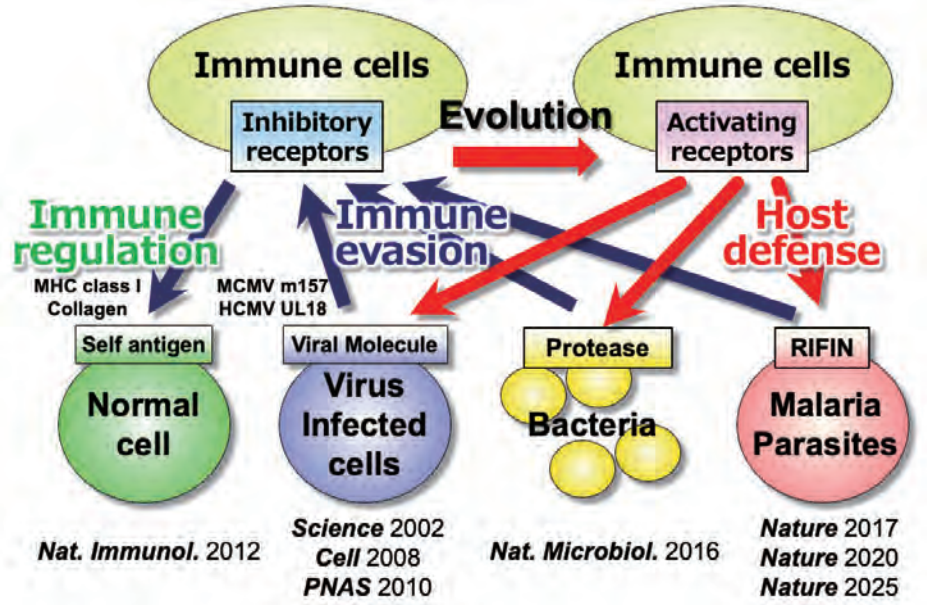


Figure 2.
Evolution of paired receptors with pathogens.
Many pathogens use immune inhibitory receptors for evasion. In contrast, immune system has acquired activating receptors to protect from these pathogens.

Recent Publications

1. Kishida K, Kawakami K, Tanabe H, Nakai W, Yonekura K, Yokoyama S, Arase H. Immune-induced TCR-like antibodies regulate specific T cell response in mice. Nature Communications 17, 3227 (2026).

2. Sakoguchi A, Chamberlain SG, Morch AM, Widdess M, Harrison TE, Dustin ML, Arase H, Higgins MK, Iwanaga S. RIFINs displayed on malaria-infected erythrocytes bind KIR2DL1 and KIR2DS1. Nature 643, 1363-1371 (2025).

3. 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).

4. 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, Matsuura Y, 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).

5. Saito F, Hirayasu K, Satoh T, Wang CW, Lusingu J, Arimori T, Shida K, Palacpac NMQ, Itagaki S, Iwanaga S, Takashima E, Tsuboi T, Kohyama M, Suenaga T, Colonna M, Takagi J, Lavstsen T, Horii T, Arase H. Immune evasion of Plasmodium falciparum by RIFIN via inhibitory receptors. Nature 552, 101-105 (2017).

Immune Regulation

Tadamitsu Kishimoto, MD/PhD
Sujin Kang, PhD

▶ Professor	Tadamitsu Kishimoto
▶ Associate Professor	Sujin Kang
▶ Assistant Professor	Hozaifa Saad Hassan Metwally
▶ Postdoctoral Fellow	1
▶ Research Assistant	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 1).

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

Pulmonary fibrosis (PF), a condition characterized by inflammation and collagen deposition in the alveolar interstitium, causes dyspnea and fatal outcomes. Pericytes are the vascular mural cells that maintain vascular homeostasis and promote angiogenesis during tissue remodeling. Although glycoprotein130 (gp130) signaling has been studied in multiple immune diseases, its roles based on precise cell types during PF are poorly understood. Here, we identified the protective role of gp130 signaling in pericytes, which inhibits PF by regulating $SiglecF^+$ neutrophils activation. By establishing bleomycin-induced PF models, we found that pericyte-specific gp130 deletion in mice (referred to as $gp130^{pKO}$ mice) shows higher mortality, accelerated collagen deposition, and increased vascular permeability in the fibrotic lung tissue, which implicates severe PF compared with control mice. Using bulk RNA sequencing, we found gp130-deficient pericytes exhibit enhanced fibrogenic activity due to the dysregulated IL-6 family protein-gp130 axis, causing aggravated pericyte-myofibroblast transition (PMT), and notably, an aggravated neutrophil activation. Single-cell RNA sequencing analysis confirmed a specific neutrophil subtype that highly express *Siglecf*, which showed an abundant population in bleomycin-induced $gp130^{pKO}$ mice compared with control mice. Deletion of this subtype alleviated the fibrosis condition in $gp130^{pKO}$ mice, suggesting a pro-immunopathological role of $SiglecF^+$ neutrophil during PF. Notably, we found that $SiglecF^+$ neutrophils were hyper-activated in the context of cytokine IL-1α in bleomycin-treated $gp130^{pKO}$ mice, while adoptive transfer of Il1a-deleted $SiglecF^+$ neutrophils into bleomycin-induced control mice can effectively inhibit fibrosis development. This finding

highlights the profibrotic role of SiglecF$^+$ neutrophils via IL-1α secretion. In addition, we uncovered the close spatial proximity between pericytes and SiglecF$^+$ neutrophils in both fibrotic mice lung tissue and human IPF patients, while a clearer mechanism underlying the pericyte-SiglecF$^+$ neutrophils interaction is still waiting to be explored. Taken together, our findings advance the crucial role of IL-6 family protein-gp130 signaling in pericytes, protecting against PF via inhibition of SiglecF$^+$ neutrophils activation.

3. Threonine Phosphorylation Redefines STAT Signaling: From Antimicrobial Defense to Tissue Restoration

Our research has uncovered, for the first time, an evolutionary-selected layer of regulation within STAT1(Signal Transducer and Activator of Transcription 1)—the major driver of interferon signaling and antiviral defense. We discovered a new phosphorylation site on a threonine residue within the protein's transactivation domain. This marks the first threonine phosphorylation identified in any STAT protein, completing the long standing map of STAT family regulation alongside the classical tyrosine and serine modifications. This newly identified threonine phosphorylation works as a molecular switch, fine tuning cell responses. It restrains excessive interferon signaling while promoting cell type and context specific immune and non immune programs. During bacterial infections, this switch enhances protective inflammatory responses at the cost of antiviral defenses—an adaptation particularly relevant for combating Gram negative bacterial infections, a World Health Organization critical priority. In a separate study, we revealed that STAT1 also acts as a mechanical sensor and transducer in the gut epithelium. When tissue integrity is compromised, STAT1 threonine phosphorylation activates protective structural programs that restore barrier function while limiting interferon induced toxicity. Together, our findings redefine STAT proteins as integrators of biochemical and biomechanical cues, opening new frontiers for precision therapies in infection and inflammation.

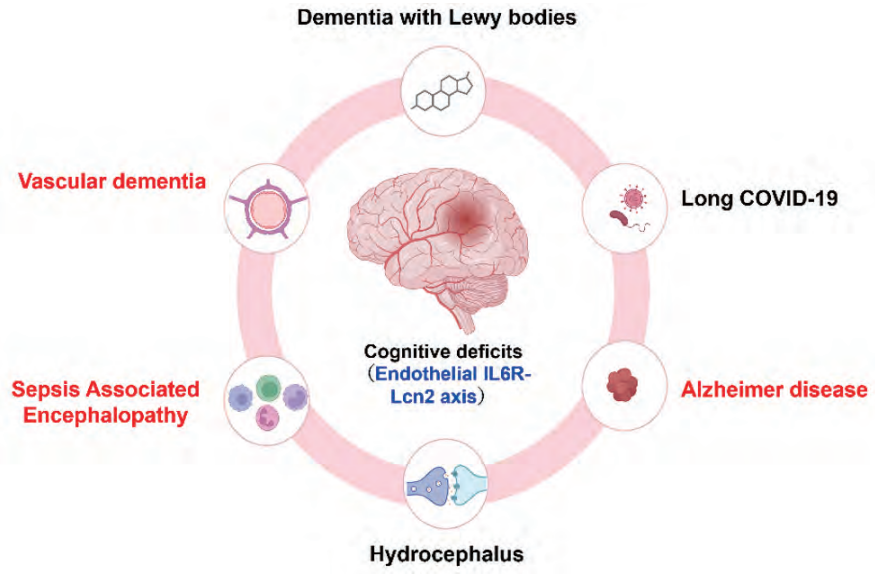


Figure.
Brain endothelial cell inflammatory responses contribute to the pathology of cognitive deficits.

Recent Publications

1. Metwally H, Elbrashy MM, Kayama H, Okuyama K, Taniuchi I, Takeda K, Kishimoto T. Threonine phosphorylation of STAT1 safeguards gut epithelial integrity and restricts interferon-mediated cytotoxicity. Proceedings of the National Academy of Sciences of the United States of America 122(30), e2511957122 (2025).

2. 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. Proceedings of the National Academy of Sciences of the United States of America 121(2), e2315898120 (2024).

3. 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, Kishimoto T. Threonine phosphorylation of STAT1 restricts interferon signaling and promotes innate inflammatory responses. Proceedings of the National Academy of Sciences of the United States of America 121(17), e2402226121 (2024).

4. 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. Proceedings of the National Academy of Sciences of the United States of America 121(16), e2315123121 (2024). (*equally corresponding author)

Mucosal Immunology

Kiyoshi Takeda, MD/PhD

▶ Professor	Kiyoshi Takeda
▶ Associate Professor	Hisako Kayama Mari Murakami
▶ Assistant Professor	Ryu Okumura Taiki Sakaguchi
▶ Postdoctoral Fellow	3
▶ Research Assistant	3
▶ Visiting Scientist	2
▶ Support Staff	2

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by recurrent intestinal inflammation driven by dysregulated adaptive immune responses. Among immune populations implicated in disease persistence and relapse, tissue-resident memory T cells (T_{RM}) have emerged as key mediators of long-term inflammatory memory within barrier tissues. Although $CD4^+$ T_{RM} accumulate in the inflamed intestinal mucosa of CD patients and exhibit potent pro-inflammatory functions, the molecular mechanisms governing their differentiation and maintenance have remained poorly defined.

In this study, we employed comprehensive single-cell multi-omics approaches to elucidate the transcriptional programs underlying pathogenic $CD4^+$ T_{RM} formation in Crohn's disease (Fig. 1). Using intestinal tissue samples from CD patients and non-inflammatory controls, we performed integrated analyses combining single-cell transcriptomics, surface protein profiling, chromatin accessibility (CITE-seq and scMultiome), and T cell receptor (TCR) sequencing. Integration of these modalities enabled the identification of a distinct $CD4^+$ T_{RM} enriched in CD lesions, characterized by coordinated upregulation of inflammatory effector genes, surface markers associated with tissue retention, and chromatin accessibility signatures indicative of disease-specific transcriptional regulation. These cells were clearly segregated from non-inflammatory T_{RM} and circulating-like populations at both transcriptomic and epigenetic levels.

Notably, transcription factor analysis identified RUNX2 and BHLHE40 as key regulators selectively upregulated in disease-associated T_{RM}. While RUNX2 is classically known as a master regulator of osteoblast differentiation, we found that CD-associated T_{RM} express an alternative transcriptional program distinct from bone-related RUNX2 activity. Chromatin accessibility profiling further demonstrated enrichment of RUNX2- and BHLHE40-associated regulatory elements, indicating their direct involvement in shaping the inflammatory T_{RM} gene network.

To investigate the developmental origin of these cells, we conducted single-cell TCR sequencing across matched intestinal mucosa, mesenteric lymph nodes, and peripheral blood from the same CD patients. A subset of disease-associated T_{RM} shared identical TCR clonotypes with circulating and lymph node T cells, suggesting that small proportion of the disease-associated T_{RM} population may be preconditioned toward a tissue-resident fate prior to intestinal entry.

Functional validation experiments supported the causal role of these transcription factors (Fig. 2). Overexpression of RUNX2 and/or BHLHE40 in $CD4^+$ T cells from healthy donors induced a disease-associated T_{RM}-like phenotype, including increased IFN-γ production and upregulation of the tissue-retention marker CD103. Conversely, knockdown of either transcription factor in CD patient–derived intestinal $CD4^+$ T cells reduced *IFNG* expression while increasing *S1PR1*, a receptor associated with tissue egress, thereby diminishing inflammatory retention within the gut.

Together, these findings establish RUNX2 and BHLHE40 as central transcriptional drivers of pathogenic gut-resident memory $CD4^+$ T cells in CD (Fig. 3). By linking transcriptional regulation to tissue residency and inflammatory persistence, this work provides mechanistic insight into how chronic intestinal inflammation is sustained at the cellular level. Importantly, targeting transcriptional programs specific to disease-associated TRM may offer novel therapeutic strategies to prevent relapse and long-term tissue damage in CD.

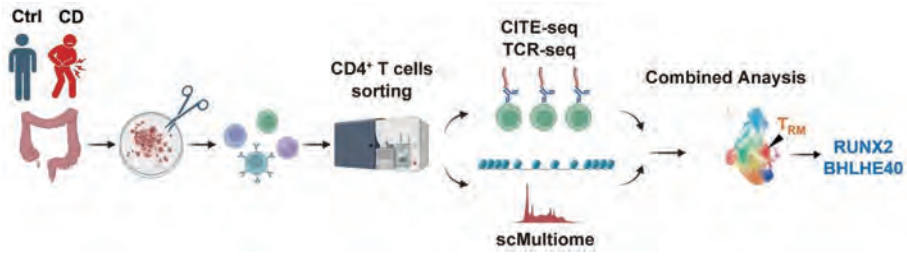


Figure 1.
Multi-omics identification of disease-associated CD4⁺ TRM.
Integrated single-cell analyses, including CITE-seq, scMultiome, and TCR sequencing, were performed on intestinal CD4⁺ T cells from CD patients and controls. The figure highlights the accumulation of IFNG⁺GZMB⁺ inflammatory TRM in CD lesions and the enrichment of RUNX2- and BHLHE40-associated transcriptional programs that define this disease-associated TRM.

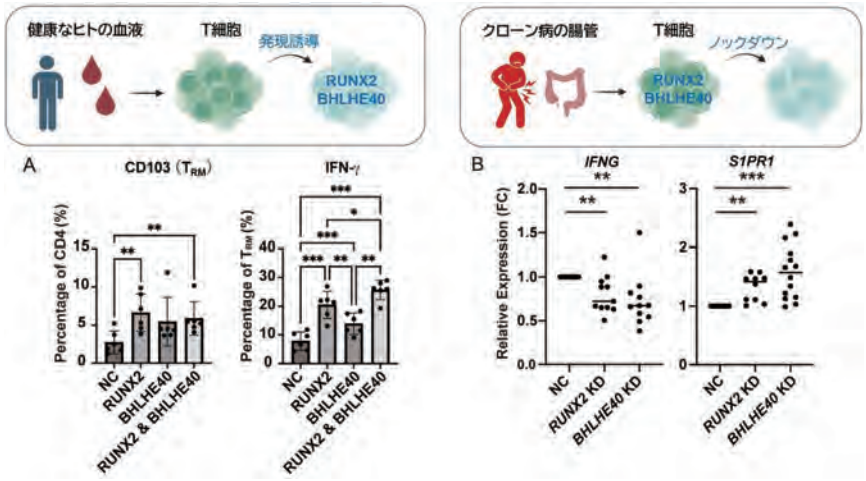


Figure 2.
Functional roles of RUNX2 and BHLHE40 in regulating TRM-associated phenotypes.
Overexpression of RUNX2 and/or BHLHE40 in healthy donor–derived CD4⁺ T cells induces TRM-like features, including increased IFN-γ production and expression of tissue-retention markers. Conversely, knockdown of these transcription factors in CD–derived intestinal CD4⁺ T cells reduces inflammatory gene expression and promotes features associated with tissue egress.

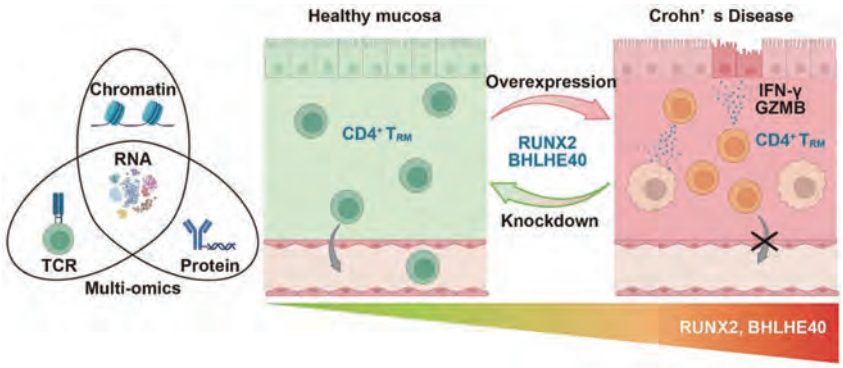


Figure 3.
Conceptual model of transcription factor–driven TRM induction in Crohn's disease.
Schematic illustration showing that upregulation of the transcription factors RUNX2 and BHLHE40 promotes the differentiation and maintenance of inflammatory gut-resident memory CD4⁺ T cells. These TRM exhibit enhanced tissue retention and effector functions, thereby contributing to chronic intestinal inflammation and disease persistence in CD.

Recent Publications

1. Arase M, Murakami M, Kihara T, et al. Multi-omics uncovers transcriptional programs of gut-resident memory CD4⁺ T cells in Crohn's disease. Journal of Experimental Medicine 222(11), e20242106 (2025).

2. Li B, Sakaguchi T, Tani H, et al. OTUD3 prevents ulcerative colitis by modulating microbiota-mediated STING activation. Science Immunology 10(109), eadm6843 (2025).

3. Oguro-Igashira E, Murakami M, Mori R, et al. The pyruvate–GPR31 axis promotes transepithelial dendrite formation in human intestinal dendritic cells. Proceedings of the National Academy of Sciences of the United States of America 121(44), e2318767121 (2024).

4. Yokoi T, Murakami M, Kihara T, et al. Identification of a unique subset of tissue-resident memory CD4⁺ T cells in Crohn's disease. Proceedings of the National Academy of Sciences of the United States of America 120(1), e2204269120 (2023).

5. Taniguchi M, Okumura R, Matsuzaki T, et al. Sialylation shapes mucus architecture inhibiting bacterial invasion in the colon. Mucosal Immunology 16(5), 624-641 (2023).

Experimental Immunology

Shimon Sakaguchi, MD/PhD

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A prevailing challenge in treating autoimmune and other inflammatory diseases is how to establish stable immune suppression and re-establish self-tolerance in an antigen-specific or a disease-specific manner. There is accumulating evidence in animal models that regulatory T cells (Tregs) specifically expressing the transcription factor Forkhead box P3 (Foxp3) in the nucleus and CD25 and CTLA-4 on the cell surface are instrumental in immune suppression and tolerance induction. Tregs are not only naturally present in the immune system (natural Tregs: nT_{regs}); they can also be induced from conventional T cells (Tconvs) in vitro (induced Tregs: iTregs) (Figure). For example, antigen stimulation of naïve $CD4^+$ Tconvs in the presence of TGF-β and IL-2 is able to convert them into antigen-specific iTregs. However, in contrast to nTregs, which are functionally stable in vivo and in vitro, iTregs are unstable, especially in inflammatory environments, and difficult to generate from effector/memory Tconvs. Nonetheless, antigen-specific iTregs are easier to prepare in vitro in large quantities as opposed to nTregs, which are resistant to in vitro expansion by antigenic stimulation. One of our projects therefore is how antigen-specific iTregs as functionally stable as nTregs can be produced in sufficient amounts not only from naïve Tconvs but also from those antigen-primed effector/memory Tconvs that are the actual culprits behind immunological diseases.

In 2025, we have shown that antigen-primed effector/memory as well as naïve Tconvs can be converted into antigen-specific Tregs by providing two conditions (Mikami et al., *Sci Transl Med*. 2025). One is the antigenic stimulation of Tconvs in the presence of a CDK8/19 inhibitor, TGF-β, and IL-2 to induce strong Foxp3 expression, the other being the deprivation of CD28 co-stimulation during iTreg generation to confer Treg-type epigenetic changes (Figure). Repeating this Treg conversion process with intermittent resting cultures with IL-2 alone efficiently yielded stably functional iTregs (S/F-iTregs) even from cytokine-producing effector T cells such as Th1, Th2, and Th17 cells. The results demonstrate that iTregs functionally similar to nTregs can be generated by manipulating specific signaling pathways, including the TGF-β/TGF-β receptor/SMAD, the IL-2/IL-2 receptor/STAT5, and the CDK8/19/STAT5 pathways for Foxp3 induction, and inhibition of the CD28/PKC/NFκB pathway for Treg-type DNA hypomethylation. The efficacy of S/F-iTreg conversion can be further increased by creating the cell culture conditions more favorable for Tregs than for Tconvs in cell expansion/survival because of distinct metabolic features of the former (e.g., less metabolic dependency of Tregs on glycolysis and glutaminolysis, hence enrichment of Tregs by reducing glucose and glutamine concentrations in the culture medium). The efficacy can also be enhanced by adding retinoic acid, dbcAMP, and dexamethasone to enrich $Foxp3^+$ cells, augment their suppressive activity, induce more IL-10 production, and reduce inflammatory cytokine production. In addition, depriving CD28 signal and supplementing ascorbate can, in combination, enhance *Foxp3* CNS2 DNA hypomethylation, ensuring stable Foxp3 expression. By incorporating these procedures into a single protocol, we have shown that mouse and human $CD4^+$ Tconvs, whether in naïve or activated effector/memory states in inflammatory states (e.g., autoimmune disease), can be converted into S/F-iTregs with high efficiency. They effectively suppressed inflammatory bowel disease, graft-versus-host disease, and pemphigus vulgaris in mouse models. Adoptive cell therapy with such effector/memory Tconv-derived S/F-iTregs may represent a strategy to achieve antigen- and disease-specific treatment of immunological diseases in humans.

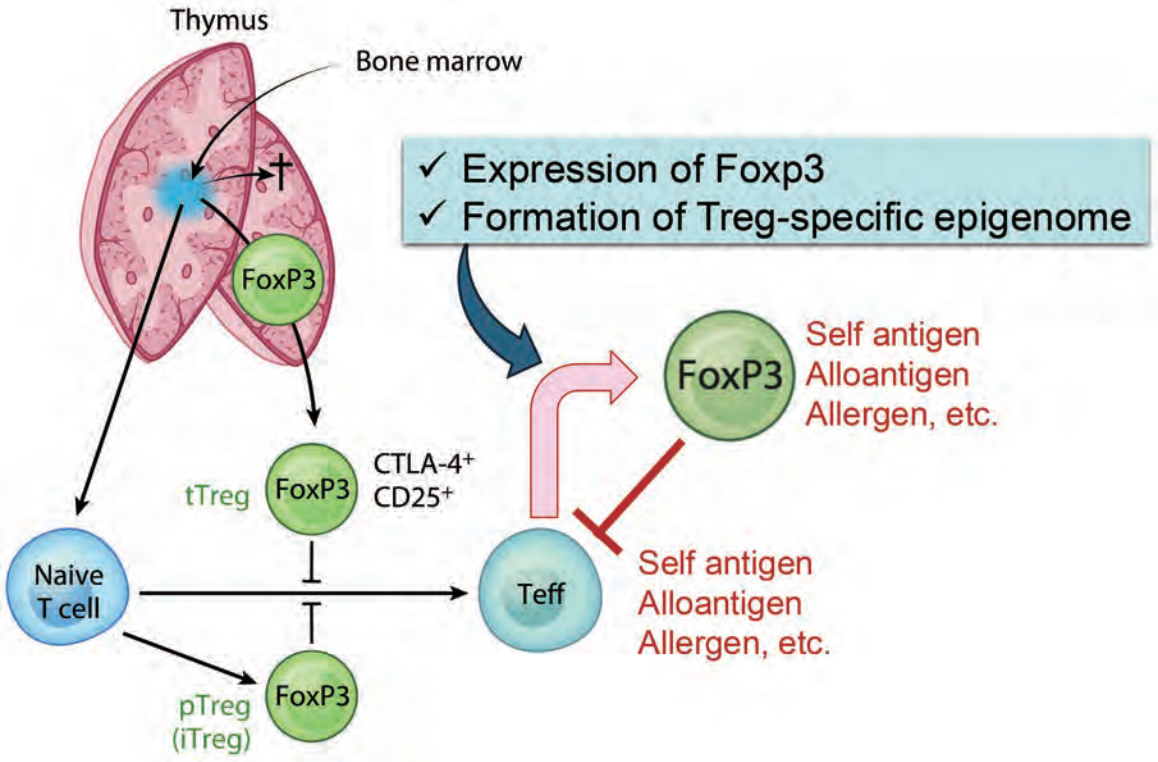


Figure.
Conversion of disease-mediating effector Tconv cells (Teff) into Foxp3⁺ Tregs for antigen-specific immune suppression/tolerance.

Recent Publications

1. Mikami N, Kawakami R, Sugimoto A, Arai M, Sakaguchi S. Generating functionally stable and antigen specific Treg cells from effector T cells for cell therapy of inflammatory diseases. Science Translational Medicine 17, eadr6049 (2025).

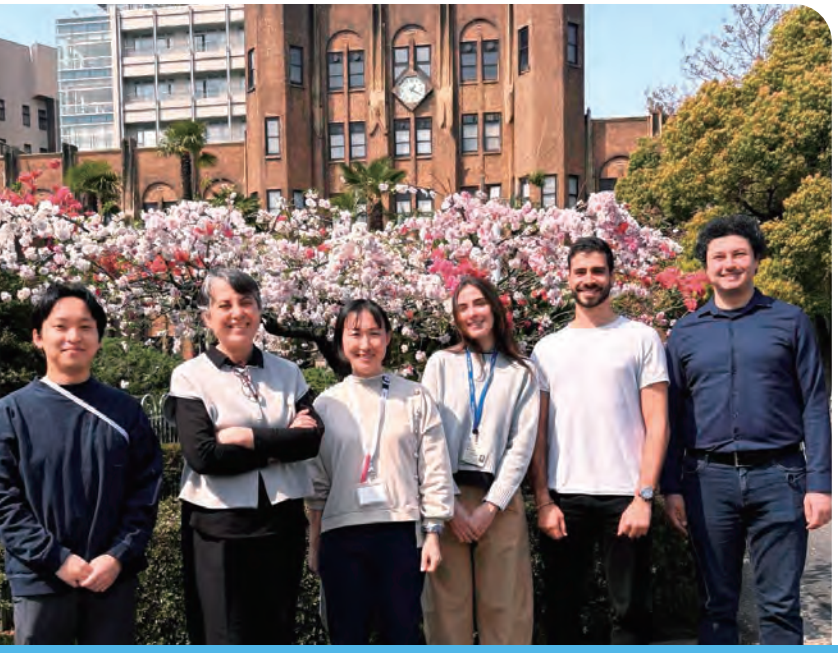
2. Chen KY, Kibayashi T, Giguelay A, Hata M, Nakajima S, Mikami N, Takeshima Y, Ichiyama K, Omiya R, Ludwig LS, Hattori K, Sakaguchi S. Genome wide CRISPR screen in human T cells reveals regulators of FOXP3. Nature 642, 191–200 (2025).

3. 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, 889–908.e13 (2025).

4. 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, 2043–2060.e10 (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 Genomics 4, 100473 (2024).

Malaria Immunology



Cevayir Coban, MD

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▶ Support Staff	1

Our laboratory focuses on elucidating the complex interactions between pathogens and the host immune system, with a central focus on malaria, particularly the immunopathogenesis of cerebral malaria. We investigate how dysregulated host immune responses contribute to severe disease outcomes, aiming to identify key mechanisms that can be targeted for intervention. A major goal of our work is to inform and accelerate the development of effective malaria vaccines by defining protective versus pathogenic immune signatures.

Cerebral malaria (CM) is a severe complication of *Plasmodium falciparum* infection, yet its precise pathogenesis remains unclear. The olfactory bulb (OB) has emerged as an important site of immunopathology in experimental cerebral malaria (ECM), though its role in disease progression is not fully defined. To address this, we performed transcriptomic profiling of the OB and identified early upregulation of interferon (IFN)-inducible GTPases, particularly Irgb6 and Gbp4, downstream of IFN-γ signaling. Using single and double knockout mice, we found that loss of these GTPases improved survival despite increased T cell infiltration into the brain, due to reduced T cell functionality and impaired antigen presentation by endothelial cells, which altered parasite accumulation in the OB. These findings demonstrate that Irgb6 and Gbp4 contribute to ECM immunopathology by modulating antigen processing, cross-presentation, and immune cell dynamics. Overall, our study finds a novel IFN-γ–driven mechanism underlying CM pathogenesis, showing how dysregulated immune responses promote inflammation and disease severity, and identifying Irgb6 and Gbp4 as potential targets for therapeutic intervention.

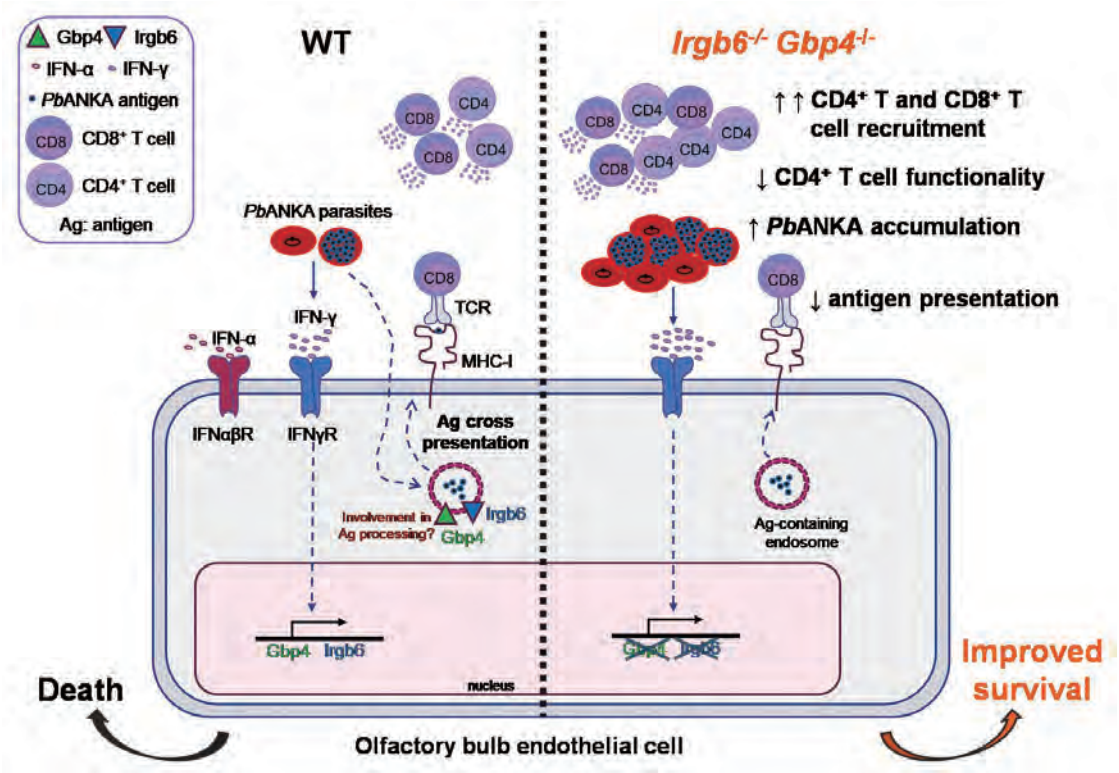

Figure.
Proposed model for the role of the GTPases Gbp4 and Irgb6 during experimental cerebral malaria in the olfactory bulb (OB). In wild-type (WT) mice, *Plasmodium berghei* ANKA (PbA) infection induces systemic IFN-γ production, which engages IFN-γ receptors on OB endothelial cells and drives the expression of Gbp4 and Irgb6. These endothelial cells subsequently process and cross-present PbA antigens to infiltrating T cells, promoting the development of ECM pathology. In contrast, Irgb6$^{-/-}$ Gbp4$^{-/-}$ mice exhibit increased parasite accumulation and enhanced infiltration of CD4^{+} and CD8^{+} T cells, but with impaired T cell functionality. The loss of Gbp4 and Irgb6 also disrupts antigen cross-presentation, indicating their critical roles in antigen processing and presentation. Collectively, these findings identify Gbp4 and Irgb6 as key regulators of immune responses in the OB, where they contribute to pathogen control but also drive excessive immune activation that leads to pathology.

Recent Publications

1. Matsuo Dapaah J, Alshaweesh J, Lee MSJ, Hayashi T, Dash R, Kuroda M, Tainaka K, Ozawa M, Kuratani A, Yamamoto M, Liu K, Fukui R, Miyake K, Kobiyama K, Rénia L, Ishii KJ, Coban C. IFNγ inducible Gbp4 and Irgb6 contribute to experimental cerebral malaria pathology in the olfactory bulb. mBio e0124925 (2025).

2. Kavian N, Kobiyama K, Ishii KJ, Coban C. Vaccine adjuvants as stand alone immunoprophylaxis in strategies for 100 day rapid responses to future pandemics. International Immunology (2025).

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. International Immunology (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. Journal of Experimental Medicine 219(2), e20211336 (2022).

5. Coban C. The host targeting effect of chloroquine in malaria. Current Opinion in Immunology 66, 98–107 (2020).

Vaccine Science

Ken J. Ishii, MD/PhD

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Our laboratory investigates the immunological mechanisms underlying vaccine responses and adjuvant activity, with a particular focus on nucleic acid-mediated innate immunity. By integrating systems vaccinology, molecular immunology, and translational research, we aim to elucidate how host- and pathogen-derived signals activate immune pathways such as cGAS-STING. These insights support the rational design of next-generation vaccines and immunotherapies targeting infectious diseases, cancer, and immune-mediated disorders.

Integrated Systems Approach for Adjuvant Discovery and Safety Evaluation

To accelerate the rational design of next-generation vaccine adjuvants, our laboratory developed a comprehensive multi-omics adjuvant evaluation platform integrating in vivo and in silico analyses. Using a panel of 25 core adjuvants, we systematically profiled immune responses across mouse and rat models, combining hematological parameters, tissue-specific transcriptomics (lymph node, liver, spleen), and public toxicogenomics datasets (Open TG-GATEs). By integrating these datasets, we established a scalable Adjuvant Database (ADB), enabling simultaneous prediction and validation of both adjuvanticity and toxicity (Natsume-Kitatani et al., *Cell Chemical Biology*, 2025). Each adjuvant exhibited a distinct gene expression signature, and machine learning-based modeling allowed cross-dataset prediction of functional properties. Notably, our analysis identified colchicine as a potential adjuvant candidate from Open TG-GATEs data, and predicted hepatotoxicity of FK565, a synthetic bacterial immunostimulant, from ADB, both of which were experimentally validated (Figure 1). These findings highlight the ability of our platform to uncover novel immunostimulatory compounds while flagging safety liabilities. This work demonstrates a new framework for large-scale, data-driven adjuvant screening, providing a foundation for precision adjuvant selection and regulatory science.

In a related study (Yoshioka et al., *NPJ Vaccines*, 2026), we demonstrated that IL-1 signaling delineates the efficacy and reactogenicity of squalene-based adjuvants in a cell-type-specific manner. Distinct IL-1-dependent pathways independently regulate protective immune responses and inflammatory side effects, providing a mechanistic basis for designing safer and more effective adjuvants.

Mechanistic Insights into cGAS-STING Activation via Nucleocytosis

In our recent study (Negishi et al., *Nature Communications*, 2026), we identified a previously unrecognized mechanism termed "nucleocytosis," in which macrophages actively extract nuclear DNA from dying cells to activate innate immune signaling. We demonstrated that lysosomal dysfunction, including proton imbalance and inhibition of PPT1, induces a unique form of cell death characterized by nuclear calreticulin accumulation. Macrophages subsequently access these altered nuclei and selectively extract DNA, triggering robust activation of the cGAS-STING-type I interferon axis. Furthermore, we showed that cationic amphiphilic drugs (CADs) can induce this process, linking pharmacological lysosomal perturbation to innate immune activation. This mechanism provides a unifying explanation for how self-DNA can drive immune responses and identifies nucleocytosis as a novel cellular pathway bridging cell death and innate immunity (Figure 2). These findings have broad implications

for antiviral immunity, cancer immunotherapy, and autoinflammatory diseases, and suggest that targeting nucleocytosis may offer new therapeutic opportunities for regulating STING-dependent inflammation.

Collectively, our studies integrate data-driven adjuvant discovery with mechanistic insights into innate immune activation. By linking systems-level analysis with cellular pathways such as nucleocytosis and STING signaling, we provide a framework for developing safe and effective immunomodulators. These efforts advance our goal of "bench to clinic to bench" research and contribute to the realization of precision vaccines and immune therapies.

100 Days Mission

Ken J. Ishii contributes to the 100 Days Mission through advisory roles in CEPI, IPPS, and G7 STEG, aiming to enable the rapid development and deployment of vaccines, diagnostics, and therapeutics within 100 days of emerging infectious threats. Our laboratory supports this global initiative by advancing adjuvant science, elucidating innate immune mechanisms, and developing platform technologies that enhance vaccine efficacy and safety. Through integration of basic immunology and translational research, we contribute to pandemic preparedness and the acceleration of next-generation countermeasures.

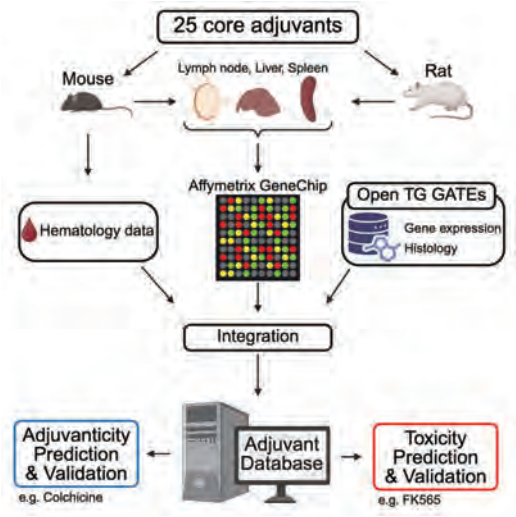

Figure 1.
Adjuvant Database Platform:
A systems vaccinology pipeline integrating multi-organ transcriptomics, hematological profiling, and public toxicogenomics datasets to predict and validate adjuvanticity and toxicity of candidate compounds.

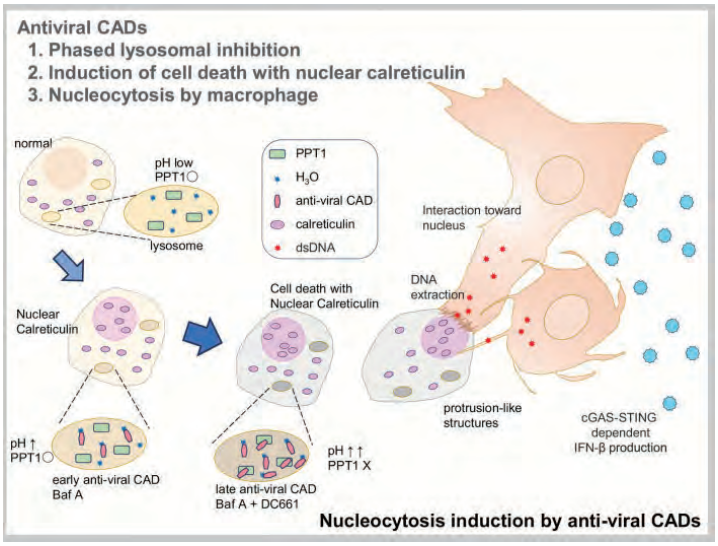

Figure 2.
Nucleocytosis Mechanism
Lysosomal dysfunction induces nuclear calreticulin accumulation and cell death, enabling macrophages to extract nuclear DNA and activate the cGAS-STING pathway, leading to type I interferon production.

Recent Publications

1. Yoshioka Y, Nishinaka-Yoshioka A, Kobiyama K, Hayashi T, Kidani Y, Yanagida Y, Kasahara J, Tsujii K, Asaoka Y, Kuroda N, Kugimiya A, Osawa H, Yoshimura A, Onishi M, Nakagawa T, Ishida S, Omoto S, Nagira M, Coban C, Ishii KJ. IL-1 delineates squalene-based adjuvant efficacy and reactogenicity in a cell-type-specific manner. NPJ Vaccines 11(1), 67 (2026).

2. Negishi H, Wada Y, Shirasaki Y, Hayashi T, Kubota Y, Iwasaki T, Kurosawa M, Ban T, Muto D, Suenaga Y, Kojima T, Matsuda Y, Irish SL, Dodo K, Suzuki T, Yamagishi M, Temizoz B, Yoshimori A, Kanai C, Nagasaki Y, Ohmuraya M, Tamura T, Iwama A, Inada T, Kuroda E, Kobiyama K, Toyama-Sorimachi N, Takekawa M, Coban C, Ishii KJ. cGAS–IFN-I responses by extracting nuclear DNA from dying cells via nucleocytosis. Nature Communications 17(1), 1658 (2026).

3. Natsume-Kitatani Y, Kobiyama K, Igarashi Y, Aoshi T, Nakatsu N, Tripathi LP, Ito J, Nyström-Persson J, Kosugi Y, Allendes Osorio RS, Nagao C, Temizoz B, Kuroda E, Standley DM, Kiyono H, Nakanishi K, Uematsu S, Hamaguchi I, Yasutomi Y, Kunisawa J, Yamasaki S, Coban C, Yamada H, Mizuguchi K, Ishii KJ. An adjuvant database for preclinical evaluation of vaccines and immunotherapeutics. Cell Chemical Biology 32(8), 1075-1088.e3 (2025).

4. Shibahara T, Temizoz B, Egashira S, Hosomi K, Park J, Surucu N, Björk A, Sag E, Doi T, Kisla Ekinci RM, Balci S, Versnel MA, Kunisawa J, Yamamoto M, Hayashi T, Ito S, Kamiyama Y, Kobiyama K, Katsikis PD, Coban C, Gursel M, Ozen S, Nishida S, Kumanogoh A, Ishii KJ. Microbial dysbiosis fuels STING-driven autoinflammation through cyclic dinucleotides. Journal of Autoimmunity 154, 103434 (2025).

5. 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).

Immunoparasitology

Masahiro Yamamoto, PhD

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	Ayumi Kuratani
▶ Research Assistant	2
▶ Support Staff	2

Alveolar macrophages (AMs) are tissue-resident macrophages that play indispensable roles in lung homeostasis. They remove inhaled foreign materials and excess surfactant in the alveolar space, thereby maintaining normal respiratory function. AMs are also known to disappear during severe pulmonary inflammation, but the biological significance of this phenomenon during infection has remained unclear. One major reason for this uncertainty is that conventional methods for AM depletion have lacked sufficient cell selectivity. Chemical depletion with clodronate liposomes can affect cells other than AMs, while previously used genetic models often alter additional myeloid populations or cause secondary changes in the lung environment, such as pulmonary alveolar proteinosis. These limitations have made it difficult to define the precise contribution of AMs to respiratory infection.

To overcome this problem, we applied our VeDTR technology to generate a transgenic mouse line in which AMs can be specifically depleted by diphtheria toxin. This system enabled us to assess AM function with substantially improved selectivity compared with previous approaches. Using this model, we examined the role of AMs in several respiratory infection settings, with particular focus on *Mycobacterium abscessus* (M. abs), a rapidly growing nontuberculous mycobacterium that is notoriously difficult to treat because of its high level of drug resistance. Since approximately half of patients with *M. abscessus* infection fail to achieve successful outcomes even after prolonged guideline-based therapy, better understanding of host defense mechanisms against this pathogen is of clear clinical importance.

Our analysis revealed that AMs prevent the proliferation of *M. abscessus* in the lung. This finding is notable because it differs from conclusions drawn from earlier studies using clodronate liposomes, which had suggested that macrophage depletion could reduce mycobacterial burden. The discrepancy strongly supports the view that the outcome of earlier depletion studies was influenced by insufficient cell specificity and possible off-target effects. By using a more selective AM depletion system, our study provides evidence that AMs are not simply passive host cells exploited by mycobacteria, but instead act as an important component of protective immunity against *M. abscessus*.

In addition to clarifying the protective role of AMs, we also investigated the meaning of their disappearance during pulmonary infection. Our results showed that the loss of AMs contributes to the reduction of bacterial load in the lungs. This observation suggests that AM disappearance is not merely a consequence of inflammation, but may represent a biologically meaningful event in the host response to infection. Thus, AMs appear to have a dual relevance in this setting: under homeostatic conditions and during the early phase of infection they contribute to bacterial control, while their disappearance during inflammatory progression may also participate in reshaping the pulmonary environment in a way that limits bacterial burden. This provides a new perspective on AM dynamics during respiratory infection.

We further examined the relationship between AMs and granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that is essential for AM development and maintenance. Inhaled GM-CSF has attracted attention as a potential therapy for refractory nontuberculous mycobacterial disease, and previous clinical case reports have suggested beneficial effects. However, the cellular basis of this therapeutic effect has remained uncertain. By using our AM-specific depletion system, we demonstrated that AMs are indispensable for GM-CSF-mediated protection against *M. abscessus* infection. This finding establishes a direct causal link

between AMs and the beneficial effect of GM-CSF in the lung. It also provides a mechanistic framework for understanding why inhaled GM-CSF may be effective in difficult-to-treat mycobacterial infections.

Taken together, this study establishes a new experimental platform for dissecting AM biology with high specificity and revisits the role of AMs in respiratory infection from a different perspective than previous depletion models allowed. Our findings show that AMs suppress *M. abscessus* proliferation, that their disappearance has biological significance in reducing pulmonary bacterial burden, and that they are essential mediators of GM-CSF-driven host defense. Beyond *M. abscessus*, the AM-specific VeDTR system should serve as a valuable tool for studying the roles of AMs in a broad range of respiratory infections and inflammatory lung diseases. In this sense, the present work not only resolves a longstanding technical problem in the field but also opens new opportunities for understanding pulmonary immunity and for developing host-directed therapies.

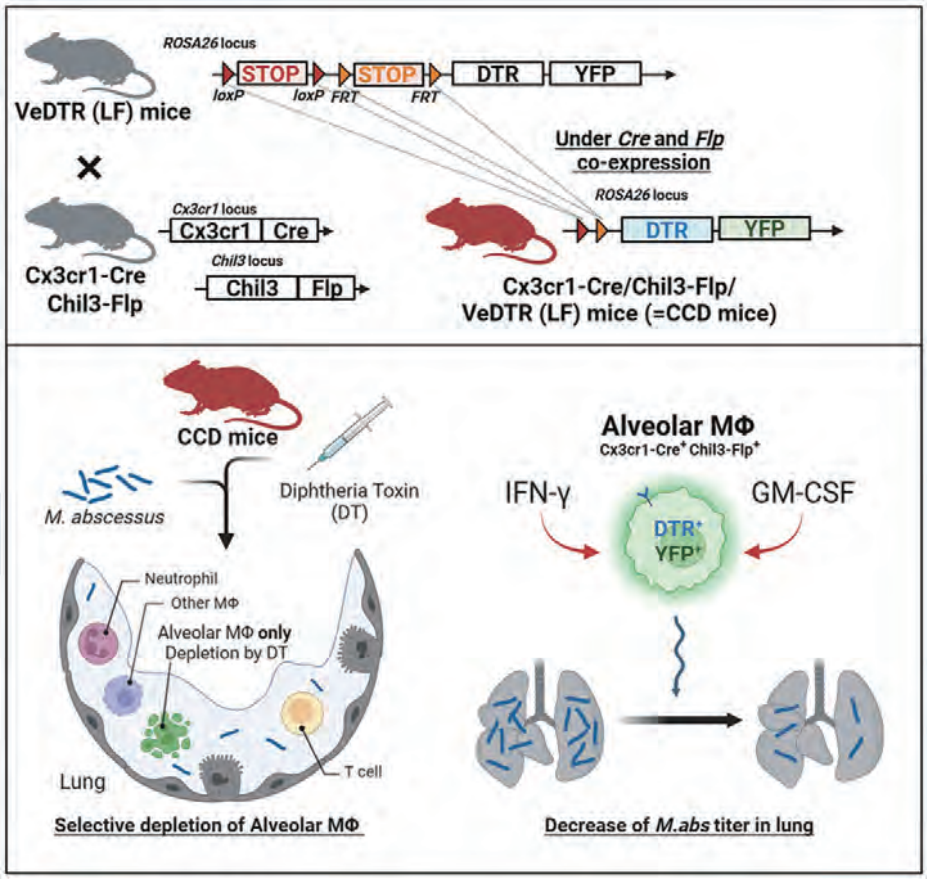

Figure.
Alveolar macrophage-targeting CCD mice reveal its role in anti-Mycobacterium immunity.

Recent Publications

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, 111975 (2025).

2. 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).

3. Okamoto M, Kuratani A, Okuzaki D, Kamiyama N, Kobayashi T, Sasai M, Yamamoto M. IFN-γ-induced Th1–Treg polarization in inflamed brains limits exacerbation of experimental autoimmune encephalomyelitis. Proceedings of the National Academy of Sciences of the United States of America 121, e2401692121 (2024).

4. Ihara F, Kyan H, Takashima Y, Ono F, Hayashi K, Matsuo T, Igarashi M, Nishikawa Y, Hikosaka K, Sakamoto H, Nakamura S, Motooka D, Yamauchi K, Ichikawa-Seki M, Fukumoto S, Sasaki M, Ikadai H, Kusakisako K, Ohari Y, Yoshida A, Sasai M, Grigg ME, Yamamoto M. Far-East Asian Toxoplasma isolates share ancestry with North and South/Central American recombinant lineages. Nature Communications 15, 4278 (2024).

5. 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 Reports 42, 112813 (2023).

Biochemistry & Immunology

Shigekazu Nagata, PhD

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

We previously identified ATP11A and ATP11C, together with their subunit CDC50A, as plasma membrane flippases (Segawa et al., *Science* 2014). Both enzymes selectively flip PtdSer, but not PtdCho. In 2021, we characterized a de novo ATP11A mutation (Q84E) in a patient with neurological deterioration (Segawa et al., *J. Clin. Invest*. 2021). This heterozygous dominant mutation altered substrate specificity, enabling ATP11A to translocate PtdCho. Aberrant PtdCho flipping led to increased SM in the outer leaflet, likely as a compensatory response.

Subsequently, we identified two additional ATP11A mutations (E114G and S399L) in patients with similar neurological phenotypes (Calianese et al., *Proc. Natl. Acad. Sci. U.S.A*. 2024). Molecular dynamics simulations suggested that these mutations enhance ATP11A affinity for PtdCho. Together, these findings highlight the importance of conserved entry and exit sites in determining flippase substrate specificity and implicate aberrant PtdCho flipping in neurological disease (Fig. 1).

Phospholipid asymmetry collapses during apoptosis and in ATP-activated macrophages. In apoptotic cells, exposed PtdSer functions as an “eat-me” signal, promoting phagocytosis either directly or via bridging molecules. This process suppresses inflammation by inhibiting IFN-α/β and TNF production while promoting TGF-β and IL-10 secretion. Although ATP11A and ATP11C are inactivated by caspases, this alone is insufficient for rapid PtdSer exposure because spontaneous lipid translocation across the membrane is energetically unfavorable. Instead, scramblases that mediate bidirectional phospholipid movement are required.

We identified TMEM16F and XKR8 as calcium- and caspase-activated scramblases, respectively (Suzuki et al., *Nature* 2010; *Science* 2013). The XKR family also includes XK, which mediates PtdSer exposure in ATP-treated macrophages (Ryoden et al., *Proc. Natl. Acad. Sci. U.S.A*. 2022), as well as XKR4 and XKR9, which show tissue-specific expression. Loss of XKR8 impairs PtdSer exposure and apoptotic cell clearance, leading to lupus-like autoimmunity or male infertility in mice (Kawano et al., *Proc. Natl. Acad. Sci. U.S.A*. 2018).

We further showed that XK forms a complex with VPS13A, a large cytoplasmic lipid transfer protein, to mediate ATP-induced phospholipid scrambling. Mutations in *XK* or *VPS13A* cause neurodegenerative disease. VPS13A binds XK via a C-terminal β-strand that engages a β-hairpin in XK, an interaction essential for scramblase activity. The XK paralogue XKR2 shares this feature and also supports scrambling. Based on analyses of VPS13A patient variants, we propose that defective PtdSer exposure impairs anti-inflammatory signaling, leading to chronic neuroinflammation and contributing to neuroacanthocytosis (Fig. 2).

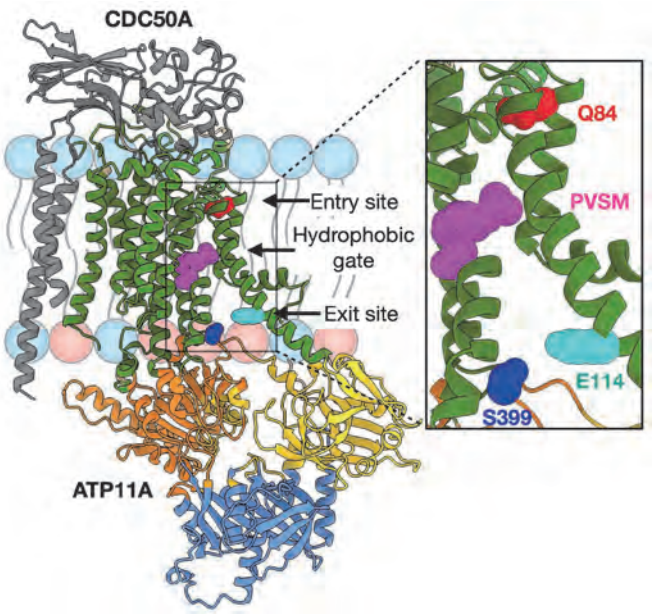

Figure 1.
Gain-of-function de novo ATP11A mutations identified in patients with neurological disorders
The ATP11A-CDC50A complex with the substrate entry/exit sites and the hydrophobic gate. PVSM residues form the hydrophobic gate. Q84 (red) is located at the entry site, while E114 (cyan) and S399 (blue)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

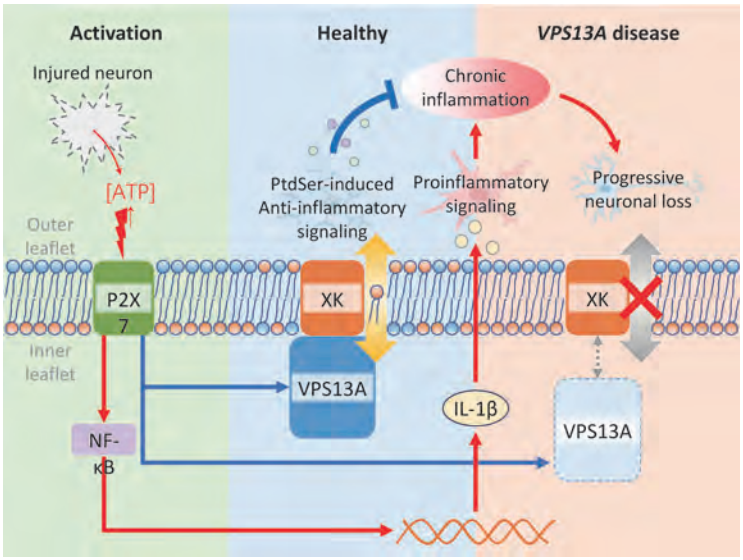

Figure 2.
A model for the neuroacanthocytosis observed in patients with VPS13A mutations. Stress-induced damage triggers ATP release, leading to local activation of P2X7 on the plasma membrane. Downstream, NF-κB promotes IL-1β secretion, whereas the VPS13A–XK complex induces PtdSer exposure, activating an anti-inflammatory pathway. Loss of scramblase activity shifts the balance toward persistent pro-inflammatory signaling, resulting in chronic inflammation.

Recent Publications

1. Lin X, Ryoden Y, Suzuki C, Ishikawa H, Sakuragi T, Uchiyama Y, Nagata S. Four subtypes of disease-causing missense mutations underlie pathogenic protein interactions in neurodegenerative VPS13A disease. Journal of Clinical Investigation 136, e200890 (2026).

2. Sakuragi T, Kanai R, Otani M, Kikkawa M, Toyoshima C, Nagata S. The role of the C-terminal tail region as a plug to regulate XKR8 lipid scramblase. Journal of Biological Chemistry 300, 105755 (2024).

3. Calianesea DC, Noji T, Sullivan JA, Schoch K, Shashi V, McNiven V, Ramos LLP, Jordanova A, Karteszi J, Ishikita H, Nagata S. Substrate specificity controlled by the exit site of human P4-ATPases, revealed by de novo point mutations in neurological disorders. Proceedings of the National Academy of Sciences of the United States of America 121, e2415755121 (2024).

4. Sakuragi T, Nagata S. Regulation of phospholipid distribution in the lipid bilayer by flippases and scramblases. Nature Reviews Molecular Cell Biology 24, 576-596 (2023).

5. Sakuragi T, Kanai R, Tsutsumi A, Narita H, Onishi E, Nishino K, Miyazaki T, Baba T, Kosako H, Nakagawa A, Kikkawa M, Toyoshima C, Nagata S. The tertiary structure of the human Xkr8–Basigin complex that scrambles phospholipids at plasma membranes. Nature Structural & Molecular Biology 28, 825-834 (2021).

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.

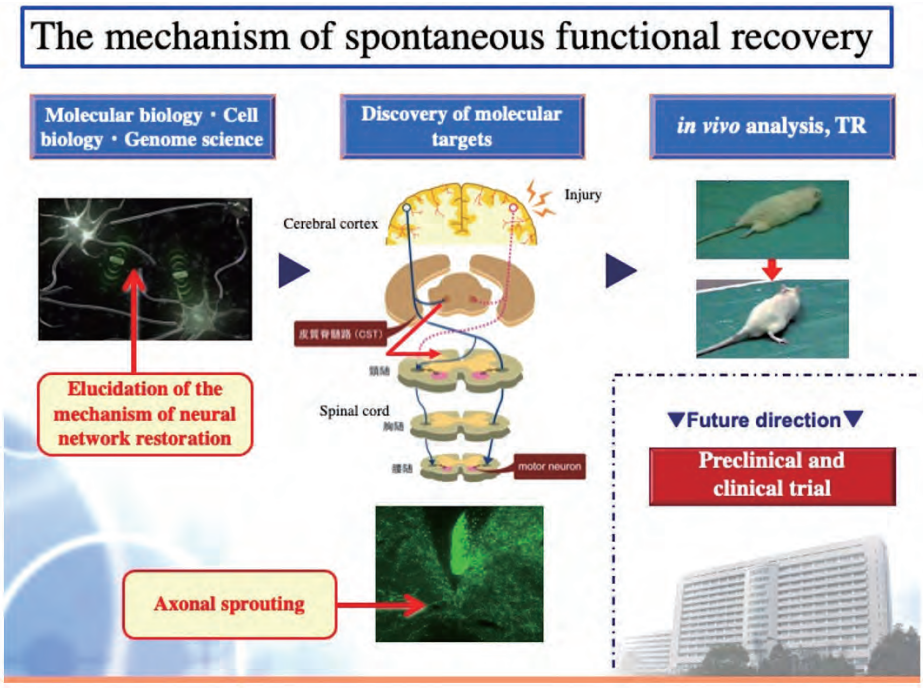


Figure 1.
The mechanism of spontaneous functional recovery.

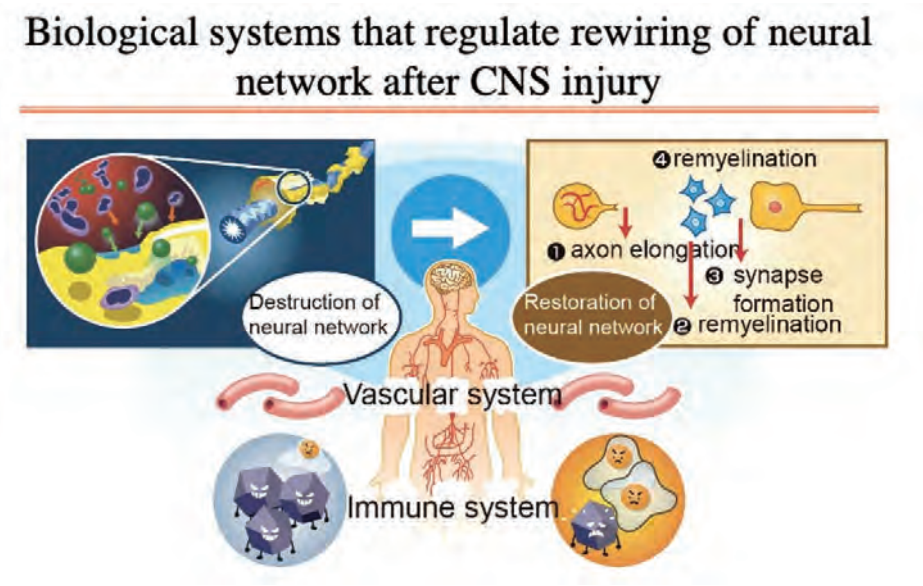


Figure 2.
Biological systems that regulate rewiring of neural network after CNS injury.

Recent Publications

1. Ashikawa Y, Itokazu T, Yamashita T. Enhancement of astrocyte regeneration through FGF8–DBX1 signaling facilitates functional recovery after pathological astrocyte loss in the spinal cord. Brain 148, 3763-3777 (2025).

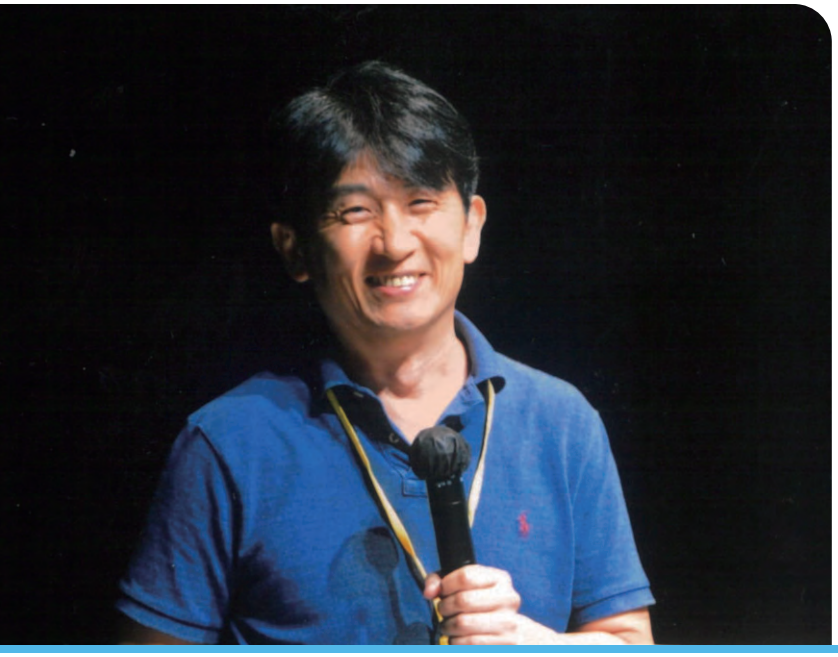
2. Shimizu M, Shiraishi N, Tada S, Sasaki T, Beck G, et al. RGMa collapses the neuronal actin barrier against disease-implicated protein and exacerbates ALS. Science Advances 9, eadg3193 (2023).

3. Iwamoto S, Itokazu T, Sasaki A, Kataoka H, Tanaka S, et al. RGMa signal in macrophages induces neutrophil-related astrocytopathy in NMO. Annals of Neurology 91, 532-547 (2022).

4. Ito M, Muramatsu R, Kato Y, Sharma B, Uyeda A, et al. Age-dependent decline in myelination capacity is mediated by apelin–APJ signaling. Nature Aging 1, 284-294 (2021).

5. Tanabe S, Yamashita T. B-1a lymphocytes promote oligodendrogenesis during brain development. Nature Neuroscience 21, 506-516 (2018).

Molecular Immunology



Sho Yamasaki, PhD

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▶ Associate Professor	Norikazu Yabuta
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▶ Support Staff	6

Invariant TCR-triggered protein kinase D activation mediates NKT cell development

Development of invariant natural killer T (iNKT) cells in the thymus requires cell-cell interaction through invariant TCR (iTCR) and CD1d, which induces expression of the transcription factor, promyelocytic leukemia zinc finger (PLZF). However, the signaling pathway linking iTCR and PLZF remains unclear. Here, we report that a serine/threonine kinase, protein kinase D (PKD), plays a pivotal role in iNKT cell development. In T cell-specific PKD-deficient (*Prkd2/3*$^{\Delta CD4}$) mice, PLZF induction and iNKT cell generation were severely impaired, which were rescued by introduction of a PLZF transgene. We identified the transcription factor Ikaros as a substrate of PKD upon iTCR stimulation. Knock-in mice carrying a phosphorylation-defective mutant Ikaros (*Ikzf1*$^{S267/275A}$) exhibited an impairment of iNKT cell development, whereas conventional T cells were normal. In iNKT cells, Ikaros binds to the upstream region of the PLZF gene to induce its transcription. Mutant mice lacking the Ikaros-binding site (Zbtb16$^{\Delta IBS}$) generated fewer iNKT cells than WT mice. These results suggest that PKD links iTCRs to PLZF induction through Ikaros, thereby mediating iNKT cell development.

Mycobacterial α-glucans hijack dectin-1 to facilitate intracellular bacterial survival

Mycobacteria have a cell envelope that can act as a shield against host defense. This study shows that mycobacteria survive in host macrophages by targeting the innate host receptor dectin-1 through a noncanonical ligand. Compared with wild-type (WT) mice, dectin-1–deficient mice were more resistant to infection to mycobacteria. Dectin-1–deficient mice presented with substantially reduced bacterial burdens, inflammatory cytokines, and infiltrating myeloid cells, such as neutrophils and macrophages. Intracellular survival of these bacteria was reduced in macrophages derived from dectin-1–deficient mice compared with those from WT mice. Cellular characterization of mycobacteria-infected macrophages indicated that the presence of dectin-1 altered phagosomal maturation and association with markers of autophagy. Activity-based purification and nuclear magnetic resonance spectrometry identified branched α-glucan as the dectin-1 mycobacterial ligand. This branched glucan was essential for activating dectin-1. These results show that mycobacterial α-glucan targets dectin-1 to facilitate intracellular bacterial survival.

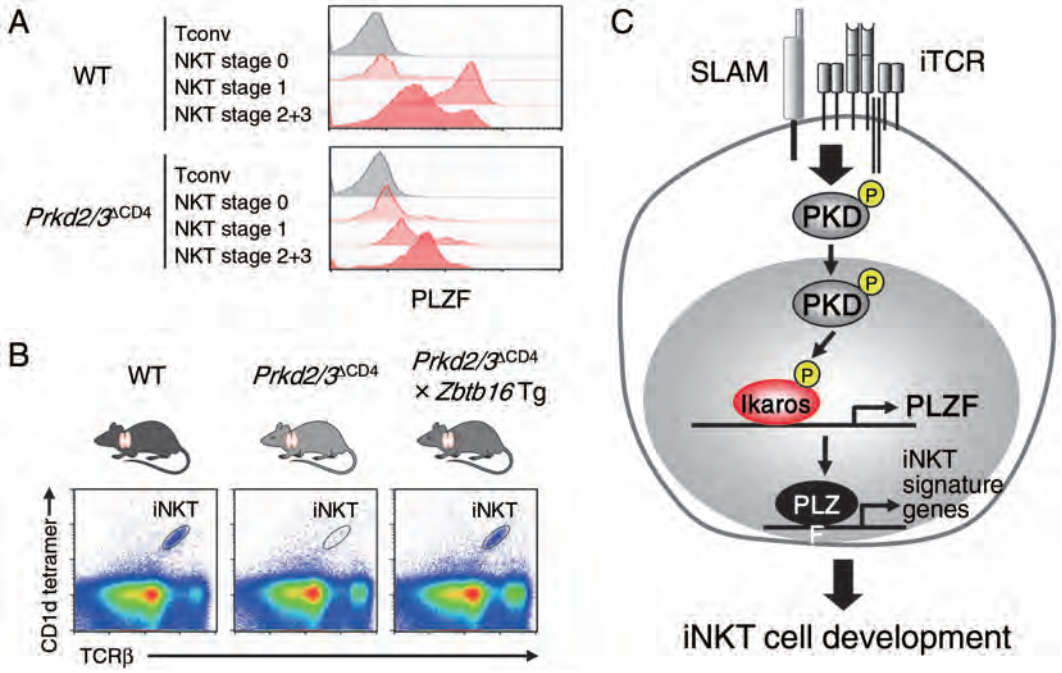

Figure.
A. Protein expression of PLZF in CD1d tetramer^{+} thymic iNKT cells at each maturation stage. PLZF induction at stage 1 was severely impaired by PKD deficiency.
B. Representative FACS profiles of iNKT cells in the thymus from WT, *Prkd2/3*$^{\Delta CD4}$ and *Prkd2/3*$^{\Delta CD4}$ × *Zbtb16* Tg mice. *Zbtb16* transgene restored iNKT cell generation in *Prkd2/3*$^{\Delta CD4}$ mice to levels comparable to WT mice.
C. PKD links iTCR to PLZF induction through phosphorylation of Ikaros thereby mediating iNKT cell development.

Recent Publications

1. Torigoe S, Salie S, Keeton R, Aylan B, Appelmelk BJ, Williams DJ, Lowman DW, Sugiki T, Matsumoto S, Kawano A, Mizuno S, Matsuo K, Sondergaad JN, Wing JB, Hoft M, Shoesmith R, Ndengane M, Coussens AK, Willment JA, Gutierrez MG, Hoving JC, Yamasaki S, Brown GD. Mycobacterial α-glucans hijack dectin-1 to facilitate intracellular bacterial survival. Science Immunology 11(115), eadw0732 (2026).

2. Ishikawa E, Kosako H, Motooka D, Imasaka M, Watarai H, Ohmuraya M, Yamasaki S. Invariant TCR-triggered protein kinase D activation mediates NKT cell development. Journal of Experimental Medicine 222, e20250541 (2025).

3. 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. Journal of Experimental Medicine 222, e20240728 (2025).

4. Sakai Y, Asa M, Hirose M, Kusuhara W, Fujiwara N, Tamashima H, Ikazaki T, Oka S, Kuraba K, Tanaka K, Yoshiyama T, Nagae M, Hoshino Y, Motooka D, Van Rhijn I, Lu X, Ishikawa E, Moody DB, Kato T, Inuki S, Hirai G, Yamasaki S. A conserved human CD4^{+} T cell subset recognizing the mycobacterial adjuvant trehalose monomycolate. Journal of Clinical Investigation 135, e185443 (2024).

5. Ito E, Inuki S, Izumi Y, Takahashi M, Dambayashi Y, Ciacchi L, Awad W, Takeyama A, Shibata K, Mori S, Mak JYW, Fairlie DP, Bamba T, Ishikawa E, Nagae M, Rossjohn J, Yamasaki S. Sulfated bile acid is a host-derived ligand for MAIT cells. Science Immunology 9, eade6924 (2024).

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 blood cells, and for 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), maintenance of the HSC pool (Sugiyama et al., *Immunity* 2006), and the development of immune cells, including B cells, plasmacytoid dendritic cells (pDCs), 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 generated mice in which the green fluorescent protein (GFP) gene was knocked into the CXCL12 locus (CXCL12-GFP mice) and identified a population of cells expressing high levels of CXCL12 within the BM, termed CXCL12-abundant reticular (CAR) cells. We found that these BM-CAR cells are the major producers of CXCL12 and SCF, and represent the 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 et al., *Immunity* 2010). Leptin receptor-expressing ($LepR^+$) cells show substantial 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 the differentiation of BM-CAR cells 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 thereby maintain HSCs and hematopoiesis in adult BM (Omatsu et al., *Nat Commun* 2022). In addition to our findings in mice, we identified the human counterpart of CAR cells, which specifically expresses CXCL12, Foxc1, and Ebf3 and constitutes the major population of nonhematopoietic 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 nonhematopoietic, non-endothelial, non-epithelial, and non-parenchymal cells that secrete structural and signaling molecules. They have traditionally been considered to form the structural components of organs and connective tissues. However, we have shown that BM-CAR cells constitute a fibroblast population characterized by salient features, including the specific expression of CXCL12 and the transcription factors Foxc1, Ebf1/Ebf3, and Runx1/Runx2, and that they 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 the maintenance of intestinal stem cells (Shoshkes-Carmel et al *Nature* 557; 242, 2018). The similarities in morphology and function between BM-CAR cells and $Foxl1^+$ telocytes raise the possibility that both originate from a common progenitor. Turley et al. recently reported a meta-analysis of 28 single-cell RNA sequencing (scRNA-seq) datasets, encompassing approximately 120,000 fibroblasts from 16 tissues, which identified a population of fibroblasts expressing high levels of the proteoglycan Dpt and Pi16 that are present in all tissues (Buechler et al., *Nature* 593; 575, 2021). 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 and $Foxl1^+$ telocytes. However, direct *in vitro* and *in vivo* evidence supporting this concept has been lacking. To obtain direct evidence, we investigated the *in vivo* potential of universal fibroblasts from various postnatal tissues to differentiate into CAR cells.

We first isolated $GFP^+PDGFR\alpha^+Sca\text{-}1^+CD34^+CD45^-Ter119^-CD31^-$ universal fibroblasts from the lung, the colon, and muscle of Ubc-GFP;CXCL12-tdTomato mice, in which the tdTomato reporter gene was knocked into the CXCL12 locus, using flow cytometry. These cells

expressed high levels of the universal fibroblast markers Pi16 and 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, in which donor-derived GFP$^+$PDGFRβ$^+$CD45$^-$Ter119$^-$CD31$^-$ cells expressed CXCL12-tdTomato at levels comparable to those in BM-CAR cells. These cells also expressed higher levels of other HSC niche factors, including CXCL12, SCF, Foxc1, Ebf3, and Runx1, than min universal fibroblasts and other cell populations.

When we co-cultured HSCs sorted from BM with either universal fibroblasts from the lung, universal fibroblasts-derived GFP$^+$CXCL12-tdTomato^{high} cells isolated from ectopic bone of mice transplanted with GFP$^+$ universal fibroblasts from the lung, or BM-CAR cells *in vitro* for 7 days, the number of HSCs increased in cultures containing universal fibroblasts-derived CXCL12-tdTomato^{high} cells compared with cultures containing universal fibroblasts. These results indicate that universal fibroblast-derived CXCL12-tdTomato^{high} cells have the potential to support HSCs *in vitro* (Figure 2).

Next, we isolated GFP$^+$ universal fibroblasts from the lung, the colon, and muscle of Ubc-GFP;CXCL12-tdTomato mice and injected them into the bone marrow of lethally irradiated recipient mice. In these experiments, we detected donor-derived GFP$^+$ cells in the recipient BM that expressed CXCL12-tdTomato at levels comparable to those in CAR cells and exhibited higher expression of other HSC niche factors, including Foxc1 and Ebf3, than other BM populations.

Together, 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).

Identification of transcription factors sufficient for the induction of CAR cells from universal fibroblasts *in vitro*

When we transduced universal fibroblasts sorted from the muscle of adult CXCL12-GFP mice with Foxc1, Ebf3, or both, which are essential for HSC niche formation, expression of CXCL12-GFP increased; however, the expression levels were much lower than those in BM-CAR cells. Thus, the transcription factors sufficient for the induction of BM-CAR cells from universal fibroblasts, which are common naive progenitors of tissue-specific fibroblasts, remain unclear.

To address this issue, we analyzed scRNA-seq datasets from developing E18.5 mouse BM cells and selected 22 transcription factors that were expressed at higher levels in CAR cell progenitors than in other nonhematopoietic cells in BM, including osteoblasts, endothelial cells, and universal fibroblasts in muscle. We then transduced universal fibroblasts sorted from the muscle of adult CXCL12-GFP mice with a mixture of the 22 genes. After 5 days of culture, a small number of cells expressing high levels of CXCL12-GFP were detected. These CXCL12-GFP^{hi} cells were sorted by flow cytometry, and the mRNA levels of the transduced genes were analyzed in individual cells. As a result, 13 transduced genes that were highly expressed in almost all CXCL12-GFP^{hi} cells were identified.

Subsequently, we transduced universal fibroblasts from the muscle of CXCL12-GFP mice with a mixture of these 13 genes. After 5 days of culture, CXCL12-GFP^{hi} cells were again sorted, and the mRNA levels of the transduced genes were analyzed in individual cells. We then identified 6 transduced genes that were highly expressed in almost all CXCL12-GFP^{hi} cells. Among these genes, we are currently attempting to identify the transcription factors sufficient for the induction of CAR cells from universal fibroblasts in vitro.

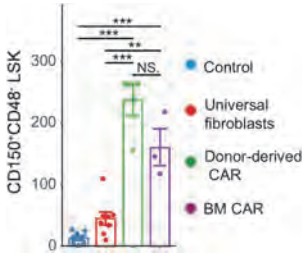

Figure 2.
Universal fibroblast-derived CXCL12-tdTomato^{high} cells have the potential to support HSCs *in vitro*.
When HSCs sorted from BM were co-cultured *in vitro* for 7 days with either universal fibroblasts from the lung, universal fibroblasts-derived CXCL12-tdTomato^{high} cells isolated from ectopic bone in mice transplanted with universal fibroblasts from the lung, or BM-CAR cells, the numbers of HSCs increased in cultures containing universal fibroblasts-derived CXCL12-tdTomato^{high} cells compared with cultures containing universal fibroblasts.

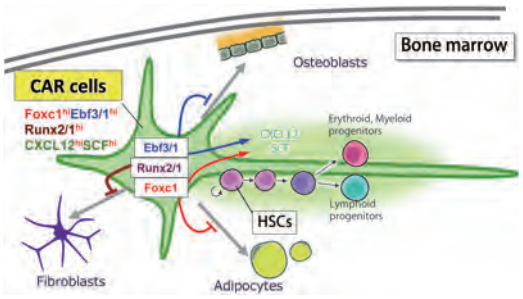

Figure 1.
Functions of BM-CAR cells.
CAR cells are the major cellular component of HSC niches and are characterized by several salient features in both mouse and human bone marrow (BM). They preferentially express the transcription factors Foxc1, Ebf1/Ebf3, and Runx1/2, as well as the cytokines CXCL12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

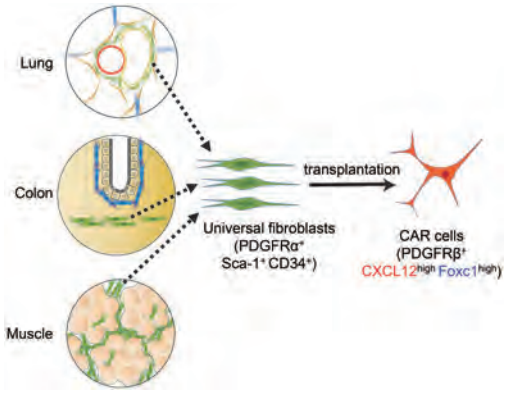

Figure 3.
In vitro differentiation of common naive progenitors into CAR cells.
Defined transcription factors and cytokines may be sufficient for the induction of CAR cells from universal fibroblasts in vitro.

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 Reports 44, 115620 (2025).
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. Nature Communications 14, 6402 (2023).
3. Omatsu Y, Aiba S, Maeta T, Higaki K, Aoki K, Watanabe H, Kondoh G, Nishimura R, Takeda S, Chung UI, Nagasawa T. Runx1 and Runx2 inhibit fibrotic conversion of cellular niches for hematopoietic stem cells. Nature Communications 13, 2654 (2022).
4. Seike M, Omatsu Y, Watanabe H, Kondoh G, Nagasawa T. Stem cell niche specific Ebf3 maintains the bone marrow cavity. Genes & Development 32, 359–372 (2018).
5. Omatsu Y, Seike M, Sugiyama T, Kume T, Nagasawa T. 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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▶ Research Assistant	2
▶ Support Staff	1

Cellular senescence is a stable form of cell-cycle arrest triggered by a variety of potentially oncogenic stresses, including telomere erosion, oxidative stress, radiation, and oncogene activation. While this response prevents the expansion of cells at risk of malignant transformation and thus functions as a tumor-suppressive mechanism, senescent cells also exert deleterious effects. They secrete pro-inflammatory factors collectively known as the senescence-associated secretory phenotype (SASP), which can promote tissue dysfunction and disease depending on the biological context. Accordingly, the selective elimination of senescent cells using "senolytic" drugs has emerged as a promising therapeutic strategy.

Over the past decade, more than 20 candidate senolytic drugs with diverse mechanisms of action have been reported, including ARV825, which we previously identified as a potent senolytic drug (Wakita et al., Nat. Commun. 2020). Despite this growing list, however, no systematic head-to-head comparison of their efficacy and specificity had been conducted. Consequently, it has remained unclear which agents most effectively eliminate senescent cells while sparing non-senescent counterparts. Furthermore, even the most potent senolytic drugs fail to eliminate a subset of resistant senescent cells, and the mechanisms underlying this resistance have remained poorly understood.

In our recent study, we systematically compared 21 senolytic agents using a quantitative Senolytic Specificity Index (SSI). This analysis identified the Bcl-2 inhibitor ABT263 and the BET inhibitor ARV825 as the most effective senolytics across fibroblast and epithelial models (Fig. 1). However, even after extended treatment with these agents, a fraction of senescent cells remained viable. We found that this resistance was associated with the maintenance of mitochondrial integrity through V-ATPase–mediated clearance of damaged mitochondria. Inducing mitochondrial stress by shifting cellular metabolism from glycolysis to oxidative phosphorylation (OXPHOS) enhanced the senolytic efficacy of ABT263 and ARV825 both *in vitro* and in mouse models. Consistently, ketogenic diet adoption or SGLT2 inhibition similarly potentiated ABT263- and ARV825-induced senolysis, resulting in reduced tumor growth and metastasis. These findings suggest that mitochondrial quality control is a key determinant of resistance to senolytic therapy and provide a framework for rational combination senotherapies (Fig. 2).

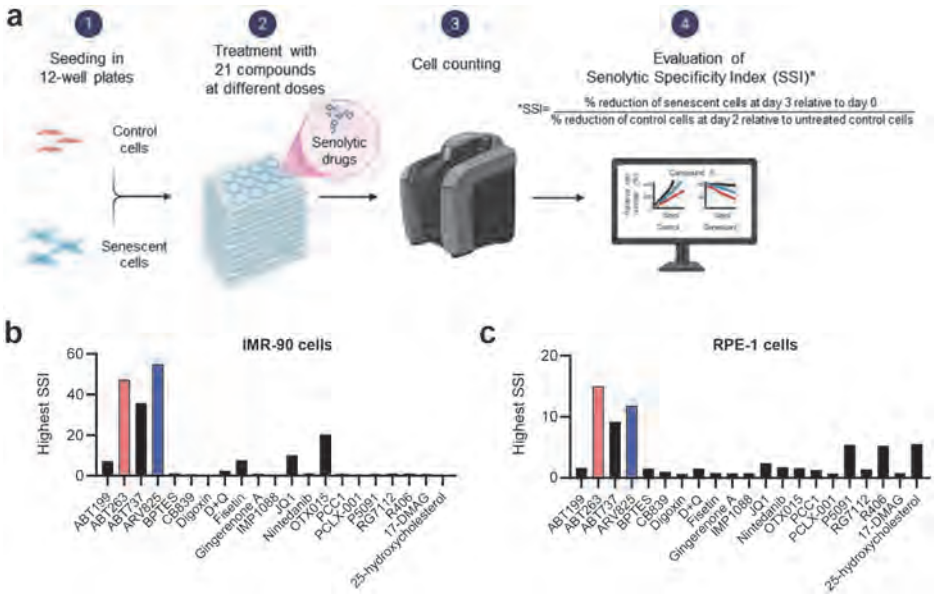

Figure 1.
Comparative analysis of senolytic drugs revealed ABT263 and ARV825 as the most potent compounds.
a, Outline of the comparative analysis of senolytic drug. Early passage HDFs (IMR-90 cells) and RPE-1 epithelial cells were rendered senescent by serial passaging (Rep-Sen cells) or treatment with 150 ng/ml doxorubicin for 10 days (DXR-Sen cells), respectively. Senescent and non-senescent (control) cells were treated with 21 compounds at multiple concentrations for 3 days. Relative cell numbers were determined throughout the experiments. The Senolytic Specificity Index (SSI) was calculated as: SSI = (% reduction of senescent cells at day 3 relative to day 0) / (% reduction of control cells at day 2 relative to untreated control cells). If the reduction of control cells at day 2 was <1%, the denominator was set to 1. Created with BioRender.com. b and c, For each compound, the SSI value at the concentration yielding the highest index is shown.

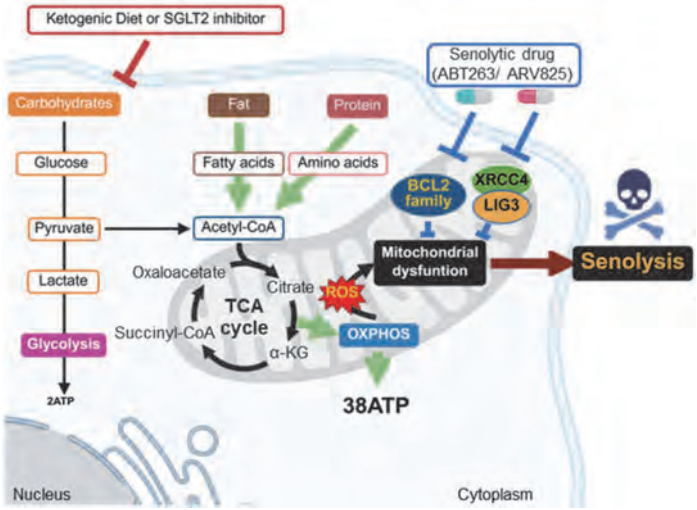

Figure 2.
Model for enhancing the senolytic activity of ABT263 and ARV825 by metabolic shift.
Ketogenic diets and SGLT2 inhibitors lower blood glucose levels, thereby suppressing glycolysis with compensatory upregulation of OXPHOS. This increases the mitochondrial workload and induces mitochondrial stress, thereby enhancing the vulnerability of mitochondria to mitochondria-targeting senolytic drugs such as ABT263 and ARV825.

Recent Publications

1. Wakita M, Ito K, Fujii K, Sakamoto D, Mikawa T, Sugawara S, Zhou X, Park JH, Miyagawa H, Motooka D, Ogasawara E, Ishihara N, Takahashi A, Kondoh H, & Hara E. Comparative analysis of senolytic drugs reveals mitochondrial determinants of efficacy and resistance. Nature Aging 6, 316-328 (2026).

2. Hara, E. Finding the point of no return for cellular senescence. Nature Cell Biology. doi.org/10.1038/s41556-023-01306-6 (2024).

3. Kawamoto S, Uemura K, Hori N, Takayasu L, Konishi Y, Katoh K, Matsumoto T, Suzuki M, Sakai Y, Matsudaira T, Adachi T, Ohtani N, Standley DM, Suda W, Fukuda S. & Hara E. Bacterial induction of B-cell senescence promotes age-related changes in the gut microbiota. Nature Cell Biology. 25:865-876 (2023).

4. Tsuji S, Minami S, Hashimoto R, et al. SARS-CoV-2 infection triggers paracrine senescence and leads to a sustained senescence-associated inflammatory response. Nature Aging 2:115-124 (2022).

Signal Transduction

Nobuyuki Takakura, MD/PhD

▶ Professor	Nobuyuki Takakura
▶ Assistant Professor	Fumitaka Muramatsu Weizhen Jia Bal Zeynep Fitriana N. Rahmawati Kensuke Hachiya
▶ Postdoctoral Fellow	2
▶ Research Assistant	6
▶ Support Staff	2

The basic role of blood vessels is to deliver oxygen and nutrients throughout the tissues, and conversely, to collect waste products and carbon dioxide from the tissues. Additionally, blood vessels allow immune cells to infiltrate tissues, playing an essential role in calming inflammation. In recent years, it has become clear that organ-specific angiocrine factors are secreted from the vascular endothelial cells of each organ, promoting the maintenance and regeneration of organ cells, and thereby maintaining the homeostasis of organs.

Blood vessels are composed of vascular endothelial cells lining the inner surface of the vessel and mural cells that support them from the basement membrane side. Vascular endothelial cells were traditionally thought to be a uniform cell type, but single-cell RNA sequencing has revealed that the vascular endothelial cells of each organ are highly heterogeneous. Previously, we showed that within existing blood vessels, there is a population of vascular endothelial stem cells, and that blood vessel formation in response to tissue damage after birth is maintained by these cells. However, the specific molecules involved in the development and maintenance of these vascular endothelial stem cells remain unclear, and it is also unknown whether such stem cells exist in humans.

Therefore, in 2025, in order to analyze the mechanisms of maintenance and differentiation of vascular endothelial stem cells, we used APJ-deficient mice, as APJ is a seven-transmembrane G protein-coupled receptor previously reported to be involved in vascular maturation, to study how APJ is associated with vascular endothelial stem cells during neovascularization in liver regeneration. Furthermore, we constructed a human iPS cell differentiation culture system to analyze whether vascular endothelial stem cells also exist in humans and whether, as seen in mice, these cells express the cell surface molecule CD157.

I: APJ Regulates the Balance Between Self-Renewal and Differentiation of Vascular Endothelial Stem Cells

CD157 marks tissue-resident vascular endothelial stem cells (VESCs) that support endothelial turnover and rapid vascular regeneration in the liver. However, mechanisms regulating postnatal VESC maintenance and differentiation remain unclear. Therefore, we investigated the role of apelin/APJ signaling using APJ knockout (KO) mice. VESCs were characterized by flow cytometry, colony-forming assays, and in vitro differentiation, while vascular regeneration was assessed after partial hepatectomy (PHx).

APJ deficiency resulted in the accumulation of VESCs in adult liver, with enhanced colony-forming capacity but impaired differentiation into mature endothelial cells. Consistently, APJ KO mice exhibited defective vascular regeneration following PHx. Transcriptomic analysis revealed increased expression of EGR1 and EGR2 and decreased Ccnd1, suggesting dysregulated cell cycle control. In addition, loss of APJ reduced Collagen IV levels, weakening the basement membrane and promoting maintenance of an undifferentiated state.

These findings demonstrate that APJ signaling is essential for balancing VESC self-renewal and differentiation. Its disruption leads to delayed differentiation and impaired vascular regeneration, highlighting the apelin/APJ pathway as a promising therapeutic target for regenerative medicine.

II: $CD157^{+}$ vascular endothelial cells derived from human-induced pluripotent stem cells have high angiogenic potential

We previously reported that a vascular endothelial stem cell population resides in pre-existing blood vessels in mice and may contribute to vascular endothelial cells in liver injury or hind limb ischemia models in the long-term. However, whether such stem cells exist in humans and can differentiate specifically into vascular endothelial cells have not been determined. We hypothesized that CD157^{+} vascular endothelial cells in humans may also possess high angiogenic potential.

First, human-derived induced pluripotent stem cells were differentiated into vascular endothelial cells and the expression of CD157 was monitored during the differentiation process. We found that CD157 emerged 11 days after the induction of differentiation, peaked at 14 days, and then declined by 24 days. We also evaluated blood vessel formation by 14- and 24-day-old vascular endothelial cells.

It was found that 14-day-old cells, when CD157 expression was at its peak, formed more blood vessels than 24-day-old cells. These results suggest that vascular endothelial cells expressing CD157 have high angiogenic potential and may exist as vascular endothelial stem cells.

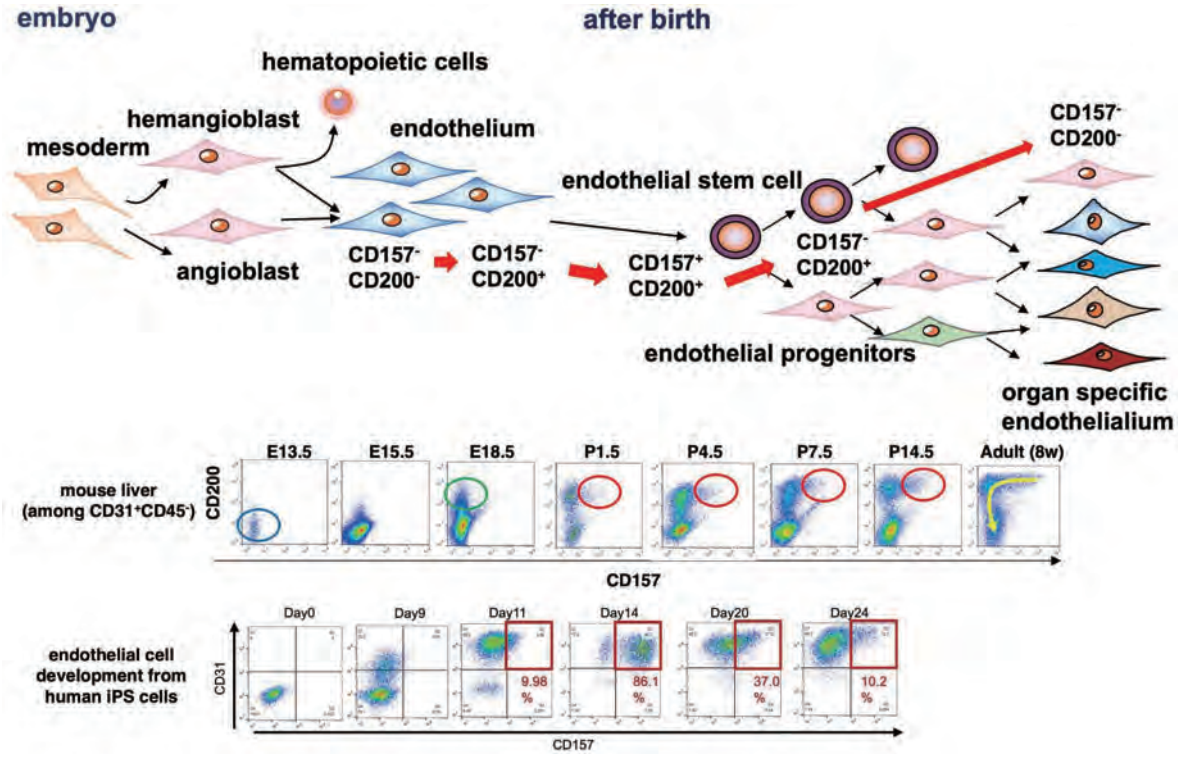

Figure.

Development of mouse and human endothelial cells.

In mice, CD157-negative vascular endothelial cells arise during early fetal development, and from this population, CD157-positive vascular endothelial stem cells emerge through reprogramming before birth. In human induced pluripotent stem (iPS) cell differentiation systems as well, CD157-negative vascular endothelial cells are initially generated, followed by the emergence of CD157-positive vascular endothelial cells with higher immaturity and strong angiogenic potential.

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. Communications Biology 7, 338 (2024).

2. Jia W, Kong L, Kidoya H, Naito H, Muramatsu F, Hayashi Y, Hsieh HY, Yamakawa D, Hsu DK, Liu FT, Takakura N. Indispensable role of Galectin-3 in promoting quiescence of hematopoietic stem cells. Nature Communications 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. Nature Communications 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. Developmental 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	6
▶ 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, vitiligo and the roles of B and T cells in immune regulation. Our research combines clinical observation, immunological investigation, genomic analysis and translational medicine to elucidate disease mechanisms and identify therapeutic targets. Recent work has highlighted effects of cytokines inhibition on immune cells, site-specific characteristics of vitiligo and genotype-phenotype correlation in TSC, a hereditary disorder.

1. Possible Role of IL-23 Inhibition in Reduction of Circulating IL-17A$^+$ CD103$^+$ Memory CD8 T Cells in Psoriasis. *Journal of Investigative Dermatology* (2025)

We explored how different biologics affect psoriasis-associated memory T-cell populations in skin and blood, with a focus on IL-17A–producing CD103$^+$ memory CD8 T cells. We analysed paired lesional (L) skin, non-lesional (NL) skin, and peripheral blood samples from 31 patients with psoriasis before and after treatment with guselkumab (IL-23 inhibitor), secukinumab (IL-17A inhibitor), or adalimumab (TNF inhibitor). We found that IL-17A$^+$ CD103$^+$ CD8 resident memory T cells (TRM) were enriched in psoriatic L skin and, to a lesser extent, in NL skin. Importantly, the proportion of these cells in NL skin increased with longer disease duration, suggesting gradual accumulation over time rather than simple reflection of current disease severity. In blood, we identified CD103$^+$ CD45RO$^+$ "ex-TRM" cells, a population thought to derive from skin-resident memory T cells. Among circulating CD8 T cells, the IL-17A–producing ex-TRM fraction was higher in patients with psoriatic arthritis than in those with psoriasis alone, and this population also tended to increase with disease duration.

A key finding was that IL-23 inhibition reduced IL-17A–producing CD8 TRM in both L and NL skin and also decreased circulating IL-17A$^+$ CD8 ex-TRM, whereas IL-17A inhibition did not show the same effect. TNF inhibition showed a possible trend but without clear statistical significance, likely because of the small sample size. We therefore propose that IL-23 blockade may act upstream by reducing pathogenic tissue-resident and skin-derived memory CD8 T-cell populations, which could help explain its potential role in limiting long-term disease persistence and possibly psoriatic arthritis development.

2. The Proposed Categorization of Vitiligo Lesions on the Hands *Pigment Cell & Melanoma Research* (2025)

Vitiligo is a common skin condition causing white patches. Although hand lesions cause significant psychological distress, clinical research remains limited. We analyzed hand lesions in 140 patients with non-segmental vitiligo and proposed a classification system based on lesion distribution. Findings showed that hand lesions were generally symmetrical, but the dominant hand was often more severely affected, suggesting that mechanical stress and the Koebner phenomenon play a role. Distal digits were involved more frequently than proximal areas and tended to worsen over time. While disease duration was the strongest predictor of severity, smoking was linked to severe distal involvement in younger patients. Cluster analysis identified four distinct subtypes: focal/scattered, distal digit, universal, and proximal digit. For instance, the focal/scattered type was common in children, whereas the universal type appeared later and responded poorly to treatment. This study highlights the

heterogeneity of hand vitiligo, suggesting that subtype-based classification can improve personalized treatment strategies.

3. Genotype–phenotype correlation for skin and neuropsychiatric features in tuberous sclerosis complex *The British journal of dermatology* (2025)

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by pathogenic variants in TSC1 and TSC2. TSC manifests as diverse symptoms across multiple organ systems and is frequently associated with neuropsychiatric symptoms. We examined genotype–phenotype correlations in 230 TSC patients, focusing on skin and neuropsychiatric symptoms. Results showed that facial angiofibromas and hypomelanotic macules, but not shagreen patches, correlated with the severity of intellectual disability, autism, and epilepsy. Age-stratified analysis indicated that severe infant macules may predict future neuropsychiatric issues, while severe neuropsychiatric disease often precedes worsening angiofibromas in adults. Whole-exome sequencing of 163 patients found no specific loci for skin severity, yet variants linked to severe neuropsychiatric phenotypes clustered in specific TSC1 and TSC2 exons, including regions within and outside the known Rap1-GAP domain. Integrating clinical and genetic data could enhance prognosis and support early, individualized TSC management.

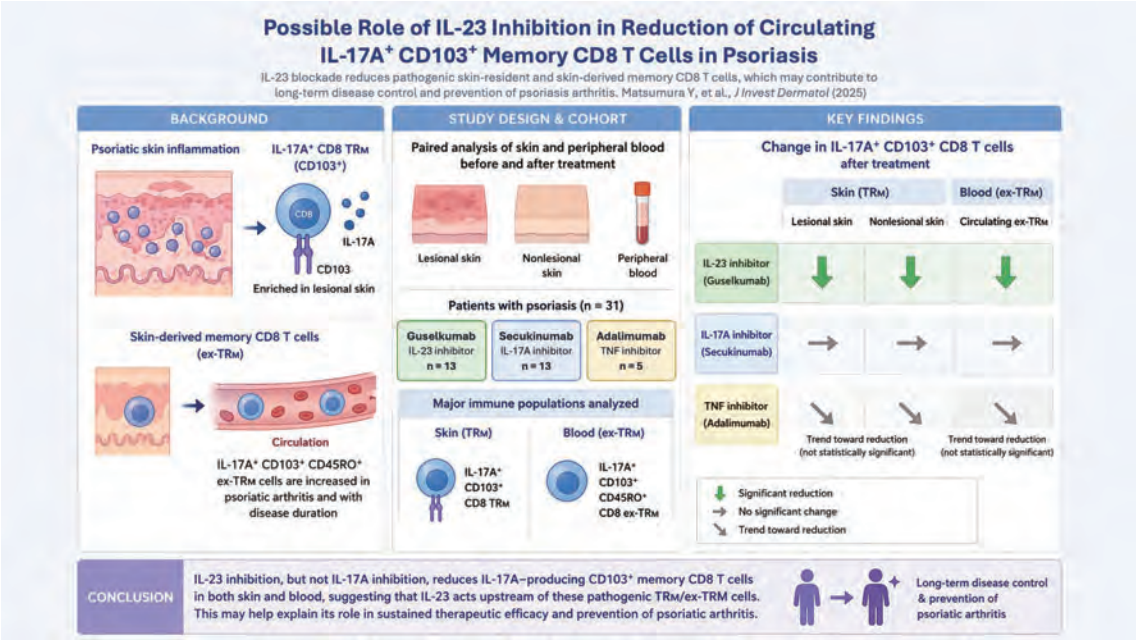

Figure.
Possible Role of IL-23 Inhibition in Reduction of Circulating IL-17A⁺ CD103⁺ Memory CD8 T Cells in Psoriasis.
IL-23 blockade reduces pathogenic skin-resident and skin-derived memory CD8 T cells, which may contribute to long-term disease control and prevention of psoriasis arthritis.

Recent Publications

1. Sonehara K, Watanabe R, Matsumura Y, et al. Whole-genome sequencing reveals rare and structural variants contributing to psoriasis and identifies CERCAM as a risk gene. Cell Genomics 5(10), 100978 (2025).

2. Matsumura Y, Kume M, Furuta J, Koguchi-Yoshioka H, Fujimoto M, Watanabe R. Possible role of IL-23 inhibition in reduction of circulating IL-17A⁺ CD103⁺ memory CD8 T cells in psoriasis. Journal of Investigative Dermatology 145(8), 2082-2085.e6 (2025).

3. Kaneda E, Koguchi-Yoshioka H, Nimura K, Hattori S, Ishino S, Fujimoto M, Wataya-Kaneda M. Genotype–phenotype correlation for skin and neuropsychiatric features in tuberous sclerosis complex. British Journal of Dermatology 192(6), 1122-1124 (2025).

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. Journal of Investigative Dermatology 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. The Lancet Rheumatology 6(2), e115-e127 (2024).

Innate Immune Systems

Kazuyo Moro, DDS/PhD

▶ Professor	Kazuyo Moro
▶ Associate Professor	Takuya Yashiro
▶ Assistant Professor	Satoshi Koga
▶ Postdoctoral Fellow	1
▶ Research Assistant	5
▶ Support Staff	2

Our laboratory has advanced research aimed at elucidating the mechanisms underlying tissue homeostasis and the pathogenesis of inflammatory diseases, with a particular focus on innate lymphoid cells. We have investigated how interactions between non-immune cells and immune cells are regulated, and how environmental cues and microbiota-derived signals shape immune responses to support tissue defense and repair.

In recent years, we have focused on immune regulatory mechanisms in barrier tissues such as the intestine lung and skin. We have conducted integrated analyses to determine how the gut microbiota and their metabolites influence immune cell function and epithelial cell differentiation. In parallel, we have extended these studies to chronic inflammatory conditions, including allergic diseases and fibrosis, with the goal of defining disease mechanisms and identifying new therapeutic strategies. During this reporting period, as part of these efforts, we conducted research on ulcerative colitis (UC).

UC is a chronic inflammatory disease of the colon, and current therapeutic strategies primarily focus on suppressing inflammation after disease onset. However, a subset of patients shows insufficient responses to existing medications and ultimately requires surgical intervention, which is associated with a marked decline in quality of life. Epidemiological studies have consistently demonstrated that appendectomy significantly reduces the risk of developing UC, yet the biological basis underlying this protective effect has remained unclear for decades.

To address this question, we established a murine model in which the cecal tip, considered the functional analogue of the human appendix, is surgically removed. Using this model, we demonstrated that cecal tip resection confers robust resistance to colitis across multiple experimental models. This protective effect is not attributable to surgical manipulation itself, but rather reflects remodeling of the intestinal environment. The cecum harbors a distinct microbial community, and its removal led to reproducible changes in the composition and functional output of the colonic microbiota. These alterations were accompanied by shifts in microbial metabolic profiles. Comprehensive metabolomic analysis identified a specific microbiota-derived oxidized lipid metabolite that was consistently increased following cecal resection. This metabolite is generated by intestinal bacteria using dietary omega-3 fatty acids as substrates. Importantly, its production depends on the presence of the microbiota, indicating that it arises from host–microbe interactions rather than host metabolism alone.

Administration of this metabolite recapitulated the protective effects of cecal resection, identifying it as a key effector of microbiota-dependent disease regulation. Mechanistically, this metabolite promoted differentiation of tuft cells in the intestinal epithelium and enhanced IL-25 production, thereby activating group 2 innate lymphoid cells (ILC2s) and inducing IL-13 production. The importance of this cascade was confirmed by the observation that colitis suppression was altered in mice deficient in tuft cells, IL-25, ILC2s, or IL-13. This pathway stimulated goblet cell differentiation and mucus secretion, leading to the formation of a robust barrier between the microbiota and the epithelial layer. In other words, the barrier reinforced by cecal resection limits epithelial exposure to luminal microbes and inflammatory stimuli, thereby suppressing the initiation and progression of inflammation. Oral administration of this metabolite significantly

ameliorated disease severity, as evidenced by reduced inflammatory cell infiltration and improved tissue architecture, reproducing the protective effect of cecal resection. Furthermore, co-administration of this metabolite with the standard UC therapy 5-ASA resulted in greater suppression of colitis than either treatment alone, indicating therapeutic synergy and potential clinical applicability.

Together, these findings reveal a previously unrecognized mechanism by which cecal resection regulates colonic immunity through microbiota-dependent metabolic signals. By linking microbial metabolism to epithelial differentiation and immune activation, this pathway provides new insight into the maintenance of intestinal homeostasis and suggests potential avenues for the development of novel therapeutic strategies.

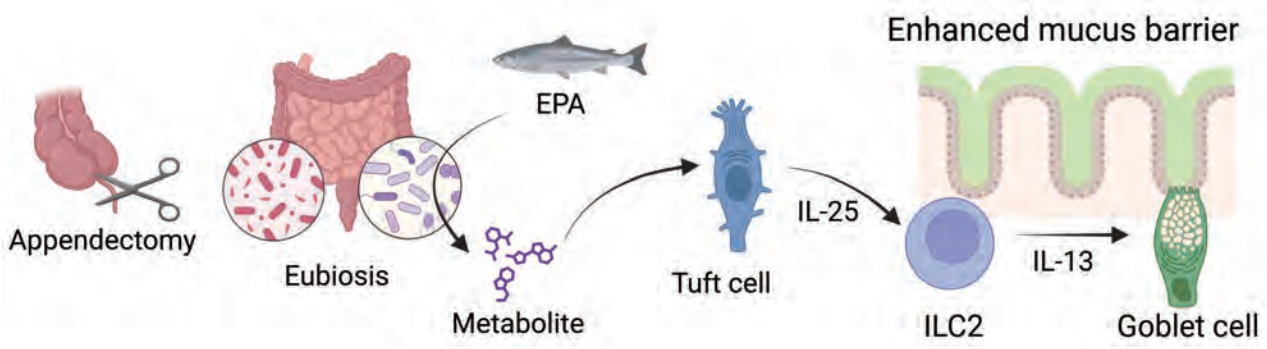

Figure.
Epithelial barrier reinforcement via the tuft cell–ILC2 axis mediated by microbiota-derived metabolism following cecal resection.
Cecal resection alters the composition of the gut microbiota, leading to changes in the profile of microbiota-derived metabolites generated through the breakdown of dietary components. These metabolites act on the intestinal epithelium to promote tuft cell differentiation. Tuft cells produce IL-25, which activates ILC2s and induces IL-13 production. IL-13, in turn, promotes goblet cell differentiation and mucus secretion, thereby reinforcing the barrier between the microbiota and the epithelial layer and contributing to the suppression of colitis.

Recent Publications

1. Yamashita M, Ogawa C, Zhang B, Kobayashi T, Nomura A, Barker C, Zou C, Yamanaka S, Hayashi KI, Shinkai Y, Moro K, Fagarasan S, Imami K, Seita J, Shirai F, Sawasaki T, Kanemaki MT, Taniuchi I. Cell-type specific, inducible and acute degradation of targeted protein in mice by two degron systems. Nature Communications 15, 10129 (2024).

2. Otaki N, Motomura Y, Terooatea T, Thomas Kelly S, Mochizuki M, Takeno N, Koyasu S, Tamamitsu M, Sugihara F, Kikuta J, Kitamura H, Shiraishi Y, Miyanohara J, Nagano Y, Saita Y, Ogura T, Asano K, Minoda A, Moro K. Activation of ILC2s through constitutive IFNγ signaling reduction leads to spontaneous pulmonary fibrosis. Nature Communications 14, 8120 (2023).

3. Kobayashi T, Moro K. Tissue-specific diversity of group 2 innate lymphoid cells in the skin. Frontiers in Immunology 13, 885642 (2022).

4. Kabata H, Motomura Y, Kiniwa T, Kobayashi T, Moro K. ILCs and allergy. Advances in Experimental Medicine and Biology 1365, 75-95 (2022).

5. Hikichi Y, Motomura Y, Takeuchi O, Moro K. Posttranscriptional regulation of ILC2 homeostatic function via tristetraprolin. Journal of Experimental Medicine 218 (2021).

Human Single Cell Immunology

James Wing, PhD

Professor	James Wing
Assistant Professor	Mara A. Llamas-Covarrubias
Postdoctoral Fellow	2

Our lab pursues multiple approaches for understanding human immunology. The first is the use of single cell analysis of the human immune cells in infectious disease and vaccine settings to understand how these immune cells are disrupted during severe disease. The second is the development of new computational tools to accelerate single cell data analysis. These two approaches are represented by our two main papers this year. Finally, we are working on new in vitro models to allow more direct experimental confirmation of cellular interactions and differentiation.

- **Discovery and characterization of a new form of T-follicular regulatory cells.**

T follicular regulatory (Tfr) cells control antibody production but the stages of their development in humans remained unclear. We discovered a previously uncharacterized subset of precursor Tfr cells (preTfr), comprising 30-50% of circulating Tfr in human blood. These preTfr are characterized by CD45RA and CXCR5 expression and, when stimulated, up-regulate suppressive molecules such as IL-1RA and show enhanced wound healing capacity. Importantly, preTfr can be expanded in vitro while retaining their suppressive capacity, suggesting they are primed for differentiation into mature Tfr. In patients with severe COVID-19 and bacterial sepsis, both preTfr and mature Tfr were significantly reduced while conventional regulatory T cells remained stable, indicating a distinct response pattern for Tfr during severe infections. Critically, the reduction in preTfr correlated with increased anti-interferon-gamma autoantibodies and activated atypical B cells (Fig 1). In contrast, SARS-CoV-2 mRNA vaccination increased both preTfr and mature Tfr frequency, particularly after later doses, suggesting that preTfr participate in well-regulated immune responses. These findings suggest that Tfr are disrupted at the earliest stage of their formation during severe disease, leading to dysregulated autoantibody production, and identify preTfr as a potential therapeutic target. (Tulyeu et al, Science Advances, 2025).

- **Development of new computational tools for single cell analysis.**

We developed scODIN (Optimized Detection and Inference of Names in scRNA-seq data), a new computational tool to automate cell type identification in single-cell RNA sequencing data. scODIN employs a tiered classification system that first identifies major cell clusters automatically, then allows users to define more granular subsets at different levels of detail (Fig 2). The tool also detects cells with intermediate phenotypes through double labelling and uses k-nearest neighbor inference to recover cells affected by dropout events. scODIN can classify 650,000 cells in just six minutes with high accuracy, significantly accelerating the analysis of complex datasets in immunology and cancer research. (Tulyeu et al, Journal of Immunology, 2025).

- **Development of new in vitro models for immune cell analysis.**

We also followed up on our previous work on new in vitro methods for measuring Treg suppressive activity (Søndergaard, et al Nat Commun. 2025) with a protocols paper (Søndergaard et al, Bio-Protocols, 2025). Our work on in vitro modelling of human cell differentiation continues as typified by our recent preprint detailing methods for induction of germinal center like B-cells from blood derived cells (Priest et al, Research Square 2025). We also extended our work identifying new B cell populations (Priest et al, Nat Commun. 2024) by providing a unified identification and sorting strategy for all B cells found in human blood (Priest and Wing, International Immunology, 2026).

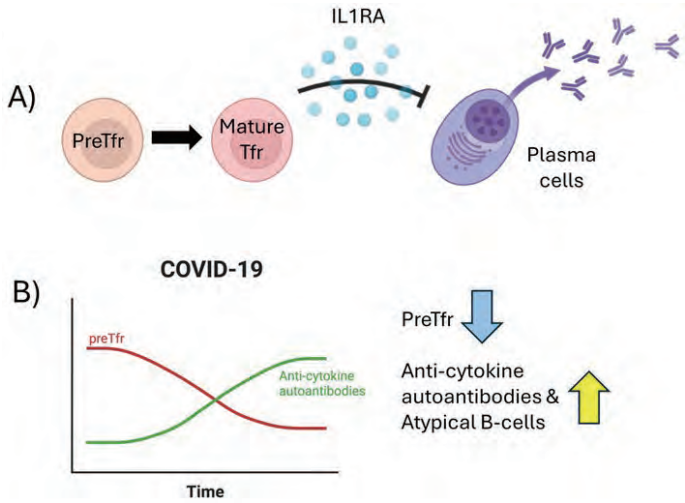

Figure 1.
Loss of preTfr during COVID-19 correlates with autoantibody production. (A) preTfr cells differentiate into mature Tfr cells, which secrete IL-1RA to suppress plasma cell formation and antibody production. (B) During severe COVID-19 infection, preTfr cell frequencies decline over time while anti-cytokine autoantibody levels increase, suggesting loss of preTfr contributes to dysregulated autoantibody production.

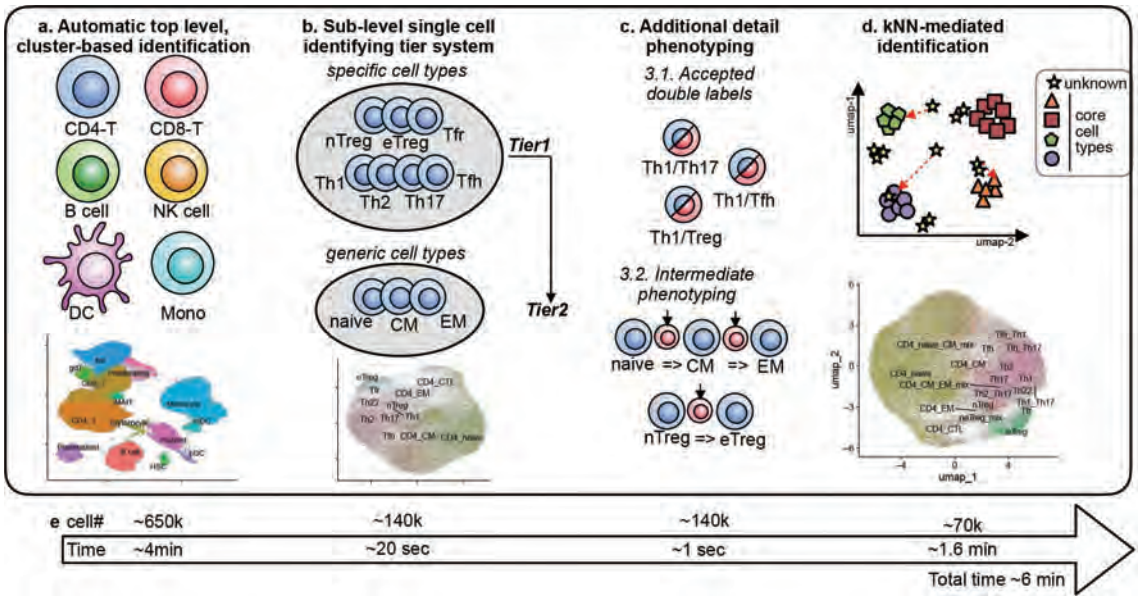

Figure 2.
scODIN (Optimized Detection and Inference of Names in scRNA-seq data) overview. a, Automatic top-level cell type identification to identify major clusters (CD4 T cells, B cells, monocytes) for further phenotyping. b, User-defined tier-based system identifies cells at different detail levels. c, Detection of accepted double labels for cells with intermediate phenotypes or transitional states between cell types. d, k-nearest neighbor (kNN) inference expands cell identification to recover cells affected by dropout.

Recent Publications

*Indicates corresponding author. †Indicates equal contributions.

1. Priest D, Wing JB.* Heterogeneity of memory B cells in human blood. International Immunology dxag006 (2026).

2. Tulyeu J, Søndergaard JN, Priest DG, Ebihara T, Matsumoto H, Llamas-Covarrubias MA, Imai M, Esaki S, Iwasaki S, Morita A, Yamazaki S, Sakaguchi S, Wing JB.* Human precursor T follicular regulatory cells are primed for differentiation into mature Tfr and disrupted during severe infections. Science Advances 11(39), eadv6939 (2025).

3. Søndergaard JN*, Tulyeu J, Priest D, Sakaguchi S, Wing JB.* Assessing human Treg suppression at single-cell resolution using mass cytometry. Bio-Protocols 15(16), e5424 (2025).

4. Tulyeu J, Priest D, Wing JB†*, Søndergaard JN†.* Optimized detection and inference of immune cell type names in scRNA-seq data. The Journal of Immunology 214(11), 3131-3142 (2025).

5. Priest D, Ise W, Wing JB.* In vitro induction of human germinal centre B cells. Research Square (Preprint) (2025).

Human Immunology (Single Cell Genomics)

Daisuke Okuzaki, PhD

▶ Associate Professor	Daisuke Okuzaki
▶ Postdoctoral Fellow	1
▶ Visiting Scientist	5
▶ Support Staff	2

Our laboratory has established a single-cell analysis platform at IFReC and serves as an NGS core facility. Building on our extensive experience during the COVID-19 pandemic, where we analyzed over 200 peripheral blood mononuclear cell (PBMC) samples as part of Team Handai, our laboratory has expanded its single-cell genomics investigations into two major infectious disease areas: dengue virus infection and SARS-CoV-2 infection (COVID-19). Through the application of single-cell RNA sequencing (scRNA-seq) and related multi-omics technologies, we aim to uncover the cellular and molecular mechanisms underlying severe infectious diseases, with a particular emphasis on immune dysregulation and host defense.

- **Dengue Virus Infection and Immune Pathogenesis:**

Severe dengue remains a cause of life-threatening complications of dengue virus (DENV) infection affecting millions worldwide, with no specific treatments available. However, the mechanisms driving vascular leakage and cytokine storm are poorly understood. Using a lethal mouse model of dengue, our analysis previously demonstrated that DENV infection induces selective expansion of γδ T cells in the small intestine, accompanied by a systemic cytokine storm involving TNF-α, IL-17, and IL-6, ultimately driving vascular leakage (Kurosu et al., PLoS Negl Trop Dis, 2023). Building on these results, we used scRNA-seq to profile immune populations in the mouse model, revealing distinct inflammatory signatures across multiple immune cell populations during severe dengue and identifying the specific cellular drivers of the cytokine storm that underlie vascular pathology (Al Kadi et al., Life Sci Alliance, 2025). Together, these results provide a detailed cellular atlas of dengue-induced immune dysregulation and highlight potential therapeutic targets for mitigating vascular leakage in severe dengue (Figure 1). Interestingly, inflammatory stromal cells also exhibited distinct, niche-specific transcriptional profiles that potentially define the local immune landscape. We are now applying spatial transcriptomics and other methods to map how the physical organization of stromal-immune interactions influences disease severity and outcomes.

- **Single-Cell Dissection of Immune Responses in COVID-19:**

Our COVID-19 research program has yielded several discoveries through single-cell approaches. First, we mapped the clonal landscape of autoantibody-secreting plasmablasts in COVID-19 patients, identifying a novel public antibody clonotype, PA-N-CoV1804, that reacts with both SARS-CoV-2 nucleocapsid protein and self-antigens (Sakakibara et al., Life Sci Alliance, 2024). This clonotype underwent *de novo* clonal expansion from naïve B cells following infection, providing new insights into the emergence of autoimmune-associated antibody responses during acute COVID-19. Second, we applied scRNA-seq combined with single-cell immune repertoire analysis to comprehensively map natural killer (NK) cell diversity in response to COVID-19 infection and mRNA vaccination (Kishi et al., Sci Rep, 2025). This study revealed dynamic shifts in NK cell subpopulations and functional states, demonstrating distinct NK cell responses between natural infection and vaccination. Third, we characterized neutrophil gene expression profiles in COVID-19 patients with acute respiratory distress syndrome (ARDS) using scRNA-seq (Ito et al., Front Immunol, 2025). Our analysis uncovered transcriptionally distinct neutrophil subsets enriched in ARDS patients, including populations with heightened inflammatory and immunosuppressive signatures, providing a granular view of

neutrophil heterogeneity in severe respiratory disease (Figure 2).

Together, these studies demonstrate the power of single-cell genomics to reveal previously unrecognized immune cell heterogeneity and molecular mechanisms underlying severe infectious diseases. By integrating scRNA-seq with spatial transcriptomics, immune repertoire profiling, and proteomics, our laboratory has generated comprehensive cellular atlases of host immune responses to dengue virus infection and COVID-19, which offer new insights into diagnostic biomarkers and therapeutic targets. Our laboratory continues to develop and apply novel sequencing technologies to bridge fundamental immunology research with clinical applications. In parallel, we maintain our role as the NGS core facility at IFReC, supporting collaborative single-cell projects across multiple research groups and clinical departments.

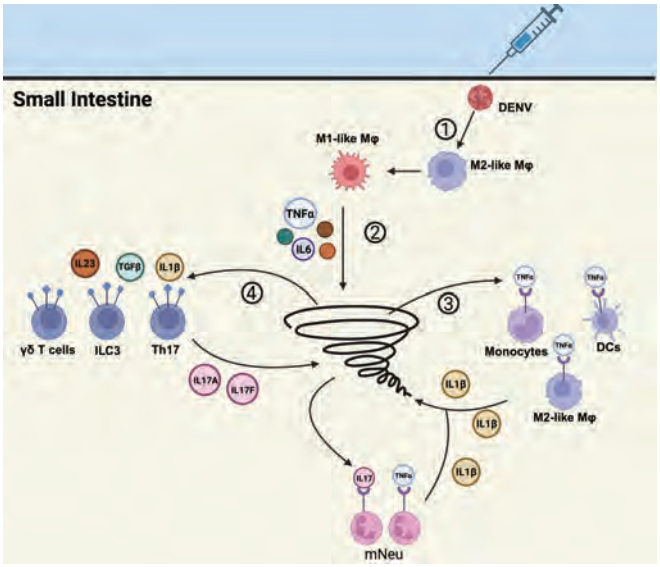

Figure 1.
Single-cell genomics elucidate immune mechanisms driving cytokine storm in severe dengue.

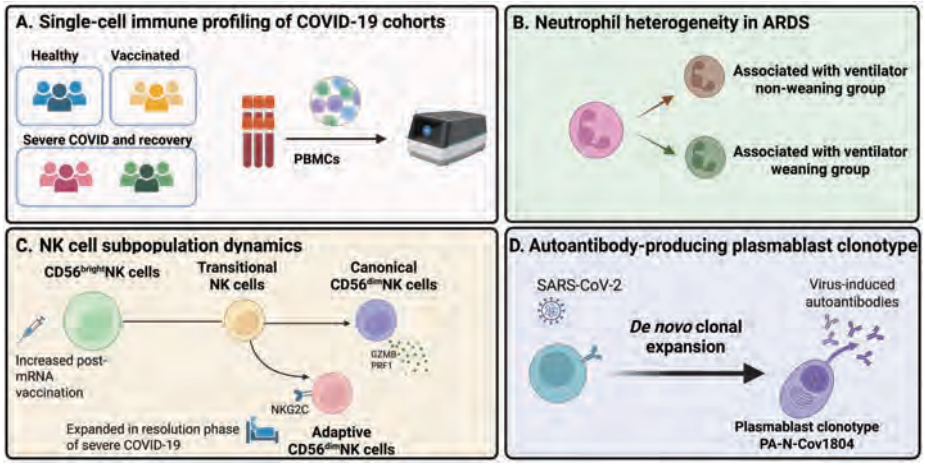

Figure 2.
Single-cell genomics reveal diverse immune cell dynamics in COVID-19.

Recent Publications

1. Ito H, Ishikawa M, Yoshimura J, Liu Y, Sakakibara S, Sugihara F, Matsumoto H, Hirata H, Ogura H, Oda J, Okuzaki D. Neutrophil gene expression in COVID-19 patients with acute respiratory distress syndrome. Frontiers in Immunology 16, 1620745 (2025).

2. Kishi Y, Liu YC, Ishikawa M, Yamashita M, Matsumoto H, Ogura H, Sakakibara S, Okuzaki D. Mapping NK cell diversity in response to COVID-19 and mRNA vaccination. Scientific Reports 15(1), 37577 (2025).

3. 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 Science Alliance 8(6), e202403008 (2025).

4. 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).

5. Sakakibara S, Liu YC, Ishikawa M, Edahiro R, Shirai Y, Haruna S, El Hussien MA, Xu Z, Li S, Yamaguchi Y, Murakami T, Morita T, Kato Y, Hirata H, Takeda Y, Sugihara F, Naito Y, Motooka D, Tsai CY, Ono C, Matsuura Y, Wing JB, Matsumoto H, Ogura H, Okada M, Kumanogoh A, Okada Y, Standley DM, Kikutani H, Okuzaki D. Clonal landscape of autoantibody-secreting plasmablasts in COVID-19 patients. Life Science Alliance 7(12), e202402778 (2024).

Cellular Immunotherapy

Naoki Hosen, MD/PhD

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▶ Associate Professor	Hisashi Kato
	Kentaro Fukushima
	Jiro Fujita
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▶ Visiting Scientist	1
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We focus on cellular immunotherapy, particularly chimeric antigen receptor (CAR) T-cell therapy for cancer. CAR T cells that target CD19 or BCMA have shown great promise in treating B-cell leukemia/lymphoma and multiple myeloma. We discovered that an integrin's active conformer may serve as a therapeutic target for multiple myeloma (MM), an incurable hematologic cancer involving the accumulation of neoplastic plasma cells in the bone marrow. Additionally, we identified R8H283, a monoclonal antibody that binds to MM cells but not normal hematopoietic or non-hematopoietic cells. R8H283 specifically recognizes CD98hc. Although CD98 heterodimers are also expressed on normal leukocytes, R8H283 does not react with them. Normal leukocytes express CD98hc glycoforms that differ from those expressed by MM cells, which may explain why R8H283 does not react with them. R8H28-derived CAR T cells exerted significant anti-tumor effects without harming normal hematopoietic cells. These findings suggest that extensive screening of primary human tumor samples may reveal cancer-specific conformational epitopes in ubiquitous proteins that cannot be identified by transcriptome or proteome analysis.

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

AML-specific target antigens are difficult to identify. Of 14,000 monoclonal antibodies (mAbs) raised against AML cells, KG2032 was identified as an mAb that binds specifically to AML cells in approximately half of patients but not to normal leukocytes, except 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 suggest that KG2032 reactivity is highly specific to AML cells in patients with KG2032-reactive HLA-DRB1 alleles who received allogeneic hematopoietic cell transplantation (allo-HCT) from a donor with nonreactive HLA-DRB1 alleles. KG2032-derived CAR T or NK cells have shown significant anti-leukemic activity, suggesting that they could potentially cure many patients with AML who are currently incurable, even with allo-HCT. We are preparing investigator-initiated clinical trials of KG2032 CAR T and CAR NK cells.

Recently, we established a novel, high-affinity monoclonal antibody (mAb) that recognizes CLL-1. CLL-1 is expressed on AML stem cells, but not on normal hematopoietic stem cells. We demonstrated that CAR T cells derived from the new anti-CLL-1 mAb exhibit a significant anti-leukemia effect in vivo. In collaboration with various cancer treatment departments at Osaka University Hospital, we have also developed CAR T and CAR NK cells to target solid tumors, such as glioblastoma. Additionally, we are focusing on developing cord blood–derived CAR NK cell therapy and improving CAR NK cell production methods.

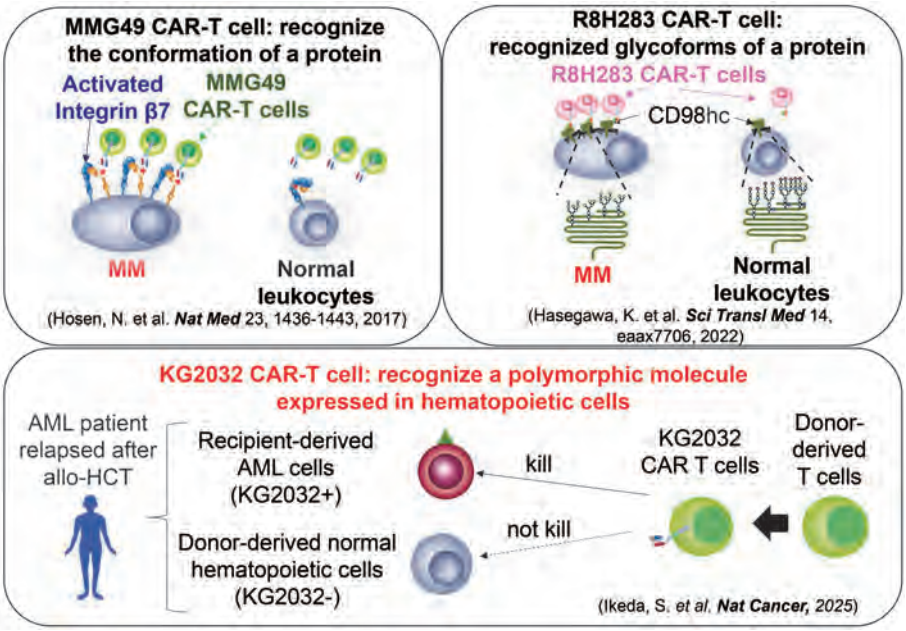

Figure 1.
New types of target antigens of CAR T cells.

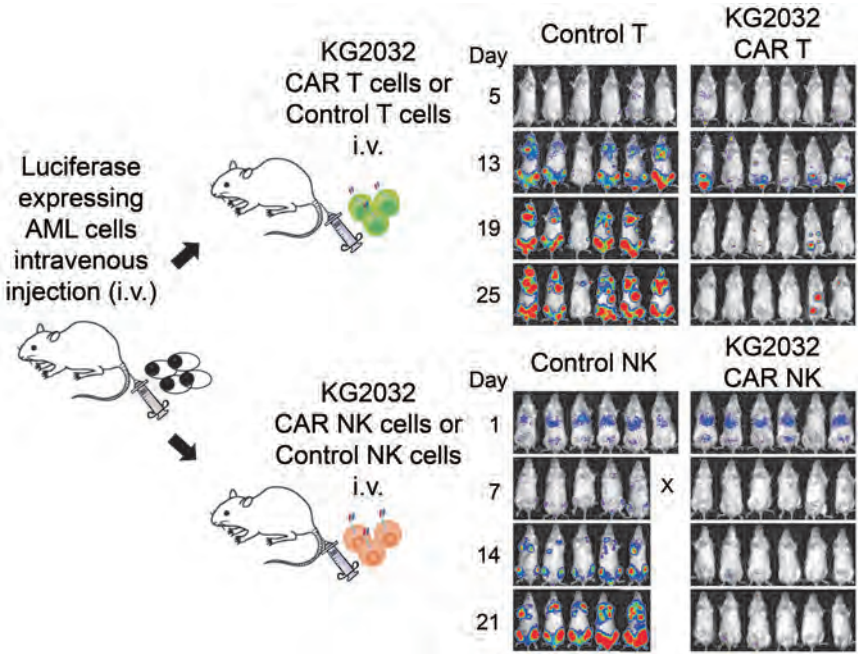

Figure 2.
Anti-leukemia effect of KG2032 CAR T or CAR NK cells in mouse xenograft models.

Recent Publications

1 Kida S, Suga M, Yamaguchi Y, Ikeda S, Kogue Y, Kawamoto R, Shibata K, Tsutsumi K, Murakami H, Mizuta E, Mizutani Y, Hosen N. CAR T cells derived from a novel, high-affinity anti-CLL-1 monoclonal antibody exhibit a significant anti-AML effect. Cancer Immunology, Immunotherapy 75, 92 (2026).

2 Ikeda S, Hasegawa K, Kogue Y, et al. CAR T or NK cells targeting mismatched HLA-DR molecules in acute myeloid leukemia after allogeneic hematopoietic stem cell transplant. Nature Cancer 6, 595–611 (2025).

3 Wibowo T, Kogue Y, Ikeda S, Yaga M, Tachikawa M, Suga M, Kida S, Shibata K, Tsutsumi K, Murakami H, Ueda Y, Kato H, Fukushima K, Fujita J, Ueda T, Kusakabe S, Hino A, Ichii M, Imai C, Okuzaki D, Kumanogoh A, Hosen N. CAR-NK cells derived from cord blood originate mainly from $CD56^{-}CD7^{+}CD34^{-}HLA\text{-}DR^{-}Lin^{-}$ NK progenitor cells. Molecular Therapy – Methods & Clinical Development 32, 101374 (2024).

4 Hasegawa K, Ikeda S, Yaga M, et al. Selective targeting of multiple myeloma cells with a monoclonal antibody recognizing the ubiquitous protein CD98 heavy chain. Science Translational Medicine 14, eaax7706 (2022).

5 Hosen N, Matsunaga Y, Hasegawa K, Matsuno H, Nakamura Y, Makita M, Watanabe K, Yoshida M, Satoh K, Morimoto S, Fujiki F, Nakajima H, Nakata J, Nishida S, Tsuboi A, Oka Y, Manabe M, Ichihara H, Aoyama Y, Mugitani A, Nakao T, Hino M, Uchibori R, Ozawa K, Baba Y, Terakura S, Wada N, Morii E, Nishimura J, Takeda K, Oji Y, Sugiyama H, Takagi J, Kumanogoh A. The activated conformation of integrin β7 is a novel multiple myeloma-specific target for CAR T cell therapy. Nature Medicine 23, 1436–1443 (2017).

Microbiology and Immunology

Nobuhiko Kamada, PhD

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▶ Associate Professor	Sho Kitamoto
	Hiroko Kitamoto
▶ Assistant Professor	Kohei Sugihara
▶ Postdoctoral Fellow	2
▶ Support Staff	4

The goal of our research program is to elucidate how host–microbe interactions influence human health and disease. We focus on the role of commensal microbiota in shaping host immunity and contributing to gastrointestinal diseases, including inflammatory bowel disease (IBD) and colorectal cancer (CRC). In particular, we aim to understand how normally benign microbes acquire pathogenic properties under disease conditions. A key concept guiding our work is that certain commensal bacteria, termed "pathobionts," become enriched during inflammation and drive disease progression. However, their identities and the mechanisms underlying their pathogenicity remain incompletely understood. To address this, we integrate microbiological, genomic, and immunological approaches to identify disease-associated pathobionts and define their functional roles.

We have identified several pathobionts associated with IBD and are investigating how they adapt to the inflamed intestinal environment. A major focus is microbial metabolic adaptation. We demonstrated that adherent–invasive *Escherichia coli* (AIEC), a representative IBD-associated pathobiont, undergoes metabolic reprogramming that enables it to colonize the epithelial niche. AIEC exploits host-derived nutrients, including amino acids enriched within epithelial cells, to support its persistence under inflammatory conditions. Our findings further show that AIEC persistence is facilitated by interactions with other microbes. For example, mucolytic bacteria such as *Akkermansia muciniphila* degrade the protective mucus barrier, allowing AIEC to access and colonize the epithelial surface. These results highlight the importance of microbial cooperation in disease pathogenesis. Based on these insights, we are developing strategies to selectively target pathobiont-specific metabolic pathways to reduce colonization and restore microbial balance in IBD.

We are also investigating the contribution of orally derived pathobionts to gastrointestinal disease. We identified oral bacteria capable of ectopic colonization in the gut, where they induce inflammation and contribute to IBD and CRC. Our work has uncovered adhesion mechanisms that enable these bacteria to adapt to the gut mucosa. We are currently pursuing microbiome-targeted approaches to eliminate these ectopically colonized pathobionts. In addition, we demonstrated that immune cells primed in the oral cavity can migrate to the gut and exacerbate inflammation. We are further characterizing these migratory immune populations and their roles in disease through the oral–gut immune axis.

Finally, we are exploring the intergenerational impact of microbiome dysbiosis. Our studies show that maternal oral dysbiosis increases the risk of IBD in offspring through vertical transmission of pathobionts. Early-life colonization of maternal pathobionts establishes long-lasting immune alterations that predispose individuals to exacerbate intestinal inflammation into adulthood.

Together, our work provides mechanistic insight into how pathobionts emerge, adapt, and contribute to disease, and supports the development of targeted microbiome-based therapies for IBD, CRC, and related disorders.

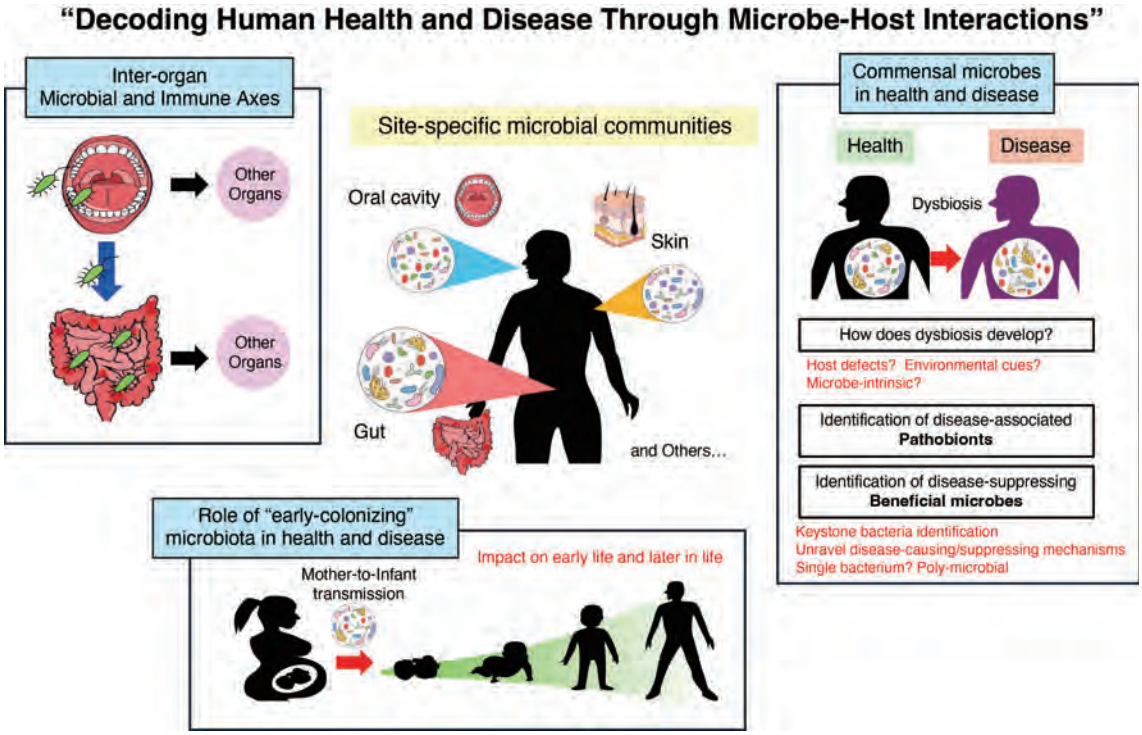

Figure.
Our goal is to unravel the complexities of human health and disease by investigating host–microbe interactions.

Recent Publications

1. Haraguchi M, Kim Y, Watanabe N, Yamazaki K, Newman KL, Gillilland MG III, Guo Y, Watanabe D, Bergin IL, Suzuki T, Motooka D, Sugihara K, Kitamoto S, Nagao-Kitamoto H, Kamada N. Transmission of maternal oral pathobionts to the infant gut predisposes offspring to exacerbated enteritis. Cell Reports 44(7), 115974 (2025).

2. Sugihara K, Kitamoto S, Saraithong P, Nagao-Kitamoto H, Hppstal M, McCarthy C, Rosevelt A, Muraleedharan CK, Gillilland MG III, 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, Jiao Y, Gillilland MG III, Hayashi A, Imai J, Sugihara K, Miyoshi M, Brazil JC, Kuffa P, Hill BD, Rizvi SM, Wen F, Bishu S, Inohara N, Eaton KA, Nusrat A, Lei YL, Giannobile WV, Kamada N. 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, Jin C, Thomsson KA, Gillilland MG III, Kuffa P, Goto Y, Jenq RR, Ishii C, Hirayama A, Seekatz AM, Martens EC, Eaton KA, Kao JY, Fukuda S, Higgins PDR, Karlsson NG, Young VB, Kamada N. Interleukin-22-mediated host glycosylation prevents Clostridioides difficile infection by modulating the metabolic activity of the gut microbiota. Nature Medicine 26(4), 608–617 (2020).

5. Kitamoto S, Alteri CJ, Rodrigues M, Nagao-Kitamoto H, Sugihara K, Himpsl SD, Bazzi M, Miyoshi M, Nishioka T, Hayashi A, Morhardt TL, Kuffa P, Grasberger H, El-Zaatari M, Bishu S, Ishii C, Hirayama A, Eaton KA, Dogan B, Simpson KW, Inohara N, Mobley HLT, Kao JY, Fukuda S, Barnich N, Kamada N. Dietary L-serine confers a competitive fitness advantage to Enterobacteriaceae in the inflamed gut. Nature Microbiology 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	1
▶ Visiting Scientist	1
▶ Support Staff	7

Our laboratory, established in November 2022, aims to elucidate the molecular, immunological, and ecological mechanisms that govern host-microbe interactions in inflammatory skin diseases, with a particular focus on atopic dermatitis (AD). Our research integrates two complementary axes: (1) early-life skin barrier and microbiome dynamics that shape disease susceptibility, and (2) evolutionary adaptation of *Staphylococcus aureus* under host and environmental pressures.

A central focus of our work is the accessory gene regulator (Agr) quorum sensing (QS) system in *S. aureus*, which coordinates virulence gene expression in a cell-density-dependent manner. We have demonstrated that Agr activity not only regulates toxin production and colonization efficiency but also critically influences host immune responses. In particular, our previous studies revealed that early-life colonization by *S. aureus* increases the risk of AD development, whereas naturally occurring Agr-deficient variants are enriched in individuals who remain disease-free. These findings suggest that variation in QS function can shift host-microbe interactions from pathogenic to commensal-like states.

We further investigated how early-life [MT1.1]skin environments shape microbial community assembly and immune development. In a prospective birth cohort, we identified that dysbiosis is already evident in neonatal skin prior to clinical onset of AD[MT2.1], characterized by an increased abundance of *Streptococcus* and a decreased abundance of *Cutibacterium acnes*. Importantly, early skincare interventions using moisturizers partially restored microbial balance, indicating that the neonatal skin ecosystem is both highly plastic and modifiable. Together, these findings highlight a critical window in which environmental and microbial factors converge to determine long-term disease risk.

Concurrently, we have expanded our investigation into the evolutionary dynamics of *S. aureus* in clinical settings. Using isolates from hospital outbreaks, we are examining how genomic [MT3.1]methylation, stress responses, and quorum sensing interact to promote bacterial persistence. Our data suggest that attenuation of Agr signaling, together with epigenetic modulation, generates "stealth" phenotypes that evade host immunity while maintaining colonization. These studies provide a framework for understanding how pathogens adapt to both host and hospital environments.

In 2025, we initiated a new translational research direction aimed at intervening in early-life immune programming. We identified PARP14 as a key regulator of type 2-skewed immune responses in neonatal skin. Using combined human cohort analyses and mouse models, we found that transient pharmacological inhibition of PARP14 during early life suppresses the development of AD-like inflammation later in life. These findings support a model in which early-life immune trajectories can be reprogrammed through short-term intervention targeting host-intrinsic pathways. A patent application has been filed based on these results.

To accelerate clinical application, we have established collaborative research programs with industry partners to develop preventive strategies for inflammatory skin diseases. These efforts focus on optimizing small-molecule inhibitors and evaluating their efficacy and safety in preclinical systems. This academia-industry integration is expected to enable the translation of mechanistic insights into actionable therapeutic approaches, particularly for early-life intervention in high-risk populations.

Looking forward, our goal is to integrate ecological and evolutionary perspectives of the skin microbiome with host-directed therapeutic strategies. By combining longitudinal human

data, multi-omics analyses, and mechanistic models, we aim to identify key determinants that govern the transition between health and allergic or infectious diseases. We define early life as a controllable window in which host immunity and microbial ecosystems can be jointly programmed to prevent disease. Ultimately, we seek to establish a new paradigm in which both microbial community dynamics and host immune programming can be modulated to prevent inflammatory diseases before their onset.

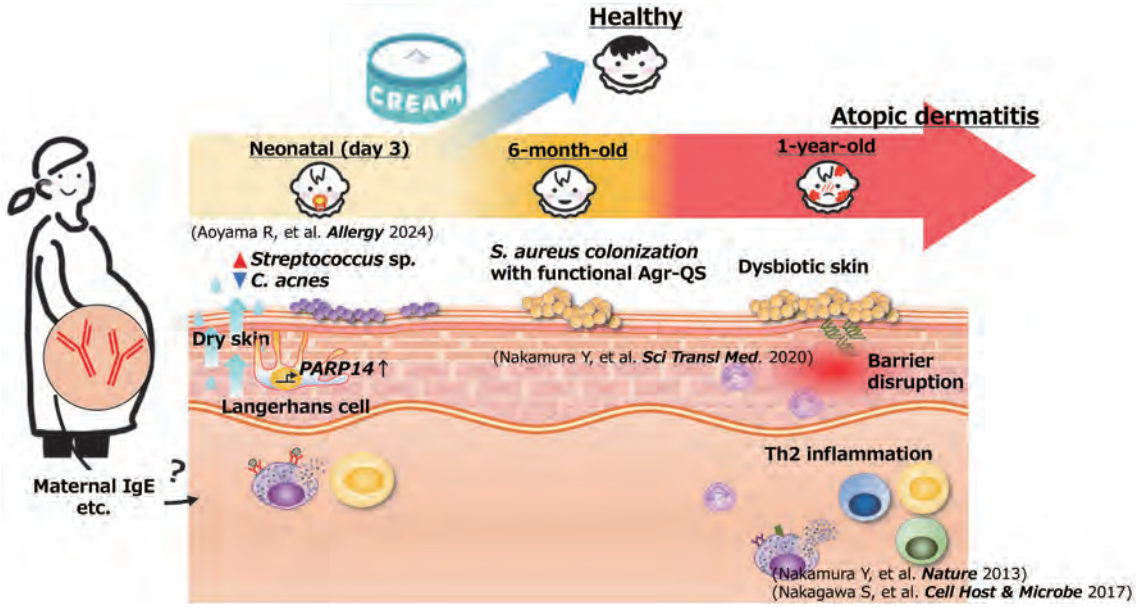

Figure.
Early-life skin microbiota dynamics in the development of atopic dermatitis.

Recent Publications

1. Yamazaki Y, Ito T, Nakagawa S, Sugihira T, Kurita Tachibana C, Villaruz AE, Ishiguro K, Salcman B, Li S, Takada S, Inohara N, Kusuya Y, Shibata A, Tamai M, Aoyama R, Inoue K, Murata S, Matsushita K, Miyabe A, Taniguchi T, Igari H, Ishiwada N, Taniguchi M, Nakada TA, Matsue H, Fujimoto M, Hishiki H, Osone Y, Hamada H, Shimojo N, Suzuki T, Otto M, Núñez G, Takahashi H, Takaya A, Nakamura Y. Altered genomic methylation promotes Staphylococcus aureus persistence in hospital environment. Nature Communications 15, 9619 (2024).

2. Aoyama R, Nakagawa S, Ichikawa Y, Inohara N, Yamazaki Y, Ito T, Sugihira T, Kono M, Akiyama M, Takahashi H, Takaya A, Ichikawa F, Nakano T, Tanaka S, Koyano Y, Fujimoto M, Núñez G, Shimojo N, Nakamura Y. Neonatal skin dysbiosis to infantile atopic dermatitis: Mitigating effects of skin care. Allergy (2024).

3. Yamazaki Y, Ito T, Tamai M, Nakagawa S, Nakamura Y. The role of Staphylococcus aureus quorum sensing in cutaneous and systemic infections. Inflammation and Regeneration 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, Inoue Y, Katayama Y, Kusuya Y, Shoji T, Takada S, Nakagawa S, Oguma R, Saito N, Ozawa N, Nakano T, Yamaide F, Dissanayake E, Suzuki S, Villaruz A, Varadarajan S, Matsumoto M, Kobayashi T, Kono M, Sato Y, Akiyama M, Otto M, Matsue H, Núñez G, Shimojo N. Staphylococcus Agr virulence is critical for epidermal colonization and associates with atopic dermatitis development. Science Translational Medicine 12(551), eaay4068 (2020).

Single Molecule Imaging

Toshio Yanagida, PhD
Ben Seymour, MD/PhD

▶ Professor	Toshio Yanagida
	Ben Seymour

Humans and animals possess remarkable capacities for self-preservation. Survival throughout life depends on the coordinated operation of two fundamental defensive systems: physiological protection mediated by the immune system, and behavioral protection mediated by the nervous system. Our research focuses on the latter—namely, the processes of behavioral homeostasis and how the brain governs actions that protect organisms from potential harm and regulate safe recuperation during recovery from infection or injury.

Although the mechanisms by which infection and injury alter behavior remain only partially understood, we propose that peripheral insults are transmitted to the brain through dedicated pathways involving unmyelinated C-fibers, ascending via brainstem and thalamic circuits to the hypothalamus and insular cortex. These regions then coordinate adaptive physiological and behavioral responses (Seymour et al., 2023).

We conceptualize this system within the framework of engineering control systems. Such systems consist of sensory pathways that detect bodily states, central control systems that determine optimal responses, and effector pathways that implement actions. We propose that the brain constructs an internal "homeostatic map" of bodily state, which is continuously updated through Bayesian-like inference processes (Mahajan et al., 2025). More recently, we have extended this framework to biomechanical contexts, modeling injury inference as a form of fault detection arising from mismatches between predicted and actual sensory consequences of movement (Mahajan et al., 2026).

An important extension of this idea comes from recent studies of molecular motors. Single-molecule studies of myosin demonstrate that biological systems can extract useful information from microscopic Brownian fluctuations and convert positional information into mechanical work. This resembles a Maxwell's demon–like principle, in which information is used to extract useful work from stochastic fluctuations. In particular, myosin selectively exploits functionally useful fluctuations embedded within Brownian motion to achieve highly efficient conversion of ATP energy into mechanical force . These findings suggest that biological systems treat noise and stochastic fluctuations not merely as errors, but as active computational resources. Furthermore, living systems may employ information-processing algorithms that are approximately one million times more energy-efficient than current AI systems and digital computers. The basis of this efficiency may lie in the selective extraction and integration of functionally meaningful fluctuations from noisy dynamics (Yanagida, et al, 2025) .

In our experimental work, we investigate how these control systems are implemented in the brain. For example, in patients with rheumatoid arthritis, we have shown that the insular cortex plays a central role in hyper-protective ("anxious") decision-making and the generation of fatigue states (Mancini et al., 2025). We have also demonstrated that altered functional connectivity within descending pain-control pathways predicts pain and fatigue in fibromyalgia, with these abnormalities tracing back to the hypothalamus, highlighting its central role in behavioral homeostasis (Kelleher et al., 2025).

Together, these findings suggest that brain-body regulation is not simply a deterministic command system, but rather an adaptive control architecture that actively utilizes fluctuations. Biological systems appear to achieve extraordinary flexibility and energy efficiency by selecting and integrating meaningful states from stochastic dynamics. This perspective has implications not only for novel treatments of pain and fatigue, but also for the

development of ultra-low-power AI and next-generation neuroengineering technologies.

Currently, we are advancing the "EPIONE" program based at the University of Oxford, while also pursuing complementary research at the IFReC Institute of the University of Osaka. Through these parallel research hubs, we are developing next-generation therapeutic technologies, including invasive brain stimulation, targeted drug delivery, and focused ultrasound systems. Looking ahead, we aim to understand how the brain and immune system cooperate to regulate injury and inflammatory states, while also uncovering the fundamental principles by which biological systems achieve ultra-efficient control by selecting meaningful information from Brownian-like fluctuations. This "information–energy conversion" perspective may ultimately provide new principles not only for treating pain and fatigue, but also for designing future AI and neuroengineering systems inspired by living organisms.

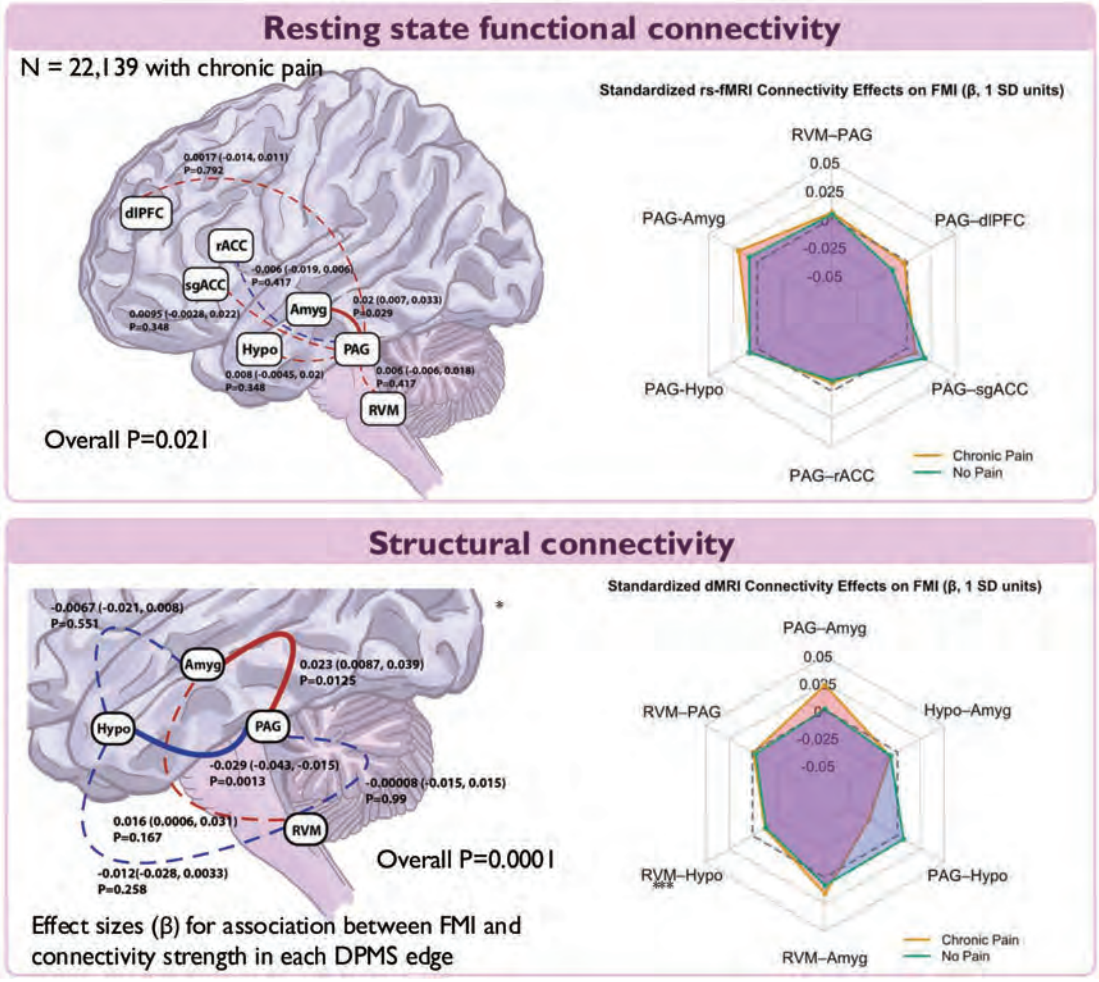

Figure.
The figure shows functional and connectivity differences associated with pain and fatigue symptoms (FMI) in the UK Biobank database. It highlights core regions associated with behavioural homeostasis and descending pain control (DPMS). Key regions include the hypothalamus (hypo), periaqueductal grey (PAG), amygdala (amyg) and the rostroventral medulla (RVM).

Recent Publications

1. Mahajan P, Dayan P, Seymour B. Homeostasis after injury: How intertwined inference and control underpin post-injury pain and behaviour. PLOS Computational Biology 22(1), e1013538 (2026).

2. Mahajan P, Tang M, Li TE, Havoutis I, Seymour B. Neural associative skill memories for safer robotics and modeling human sensorimotor repertoires. Neural Computation 38(1), 1–27 (2026).

3. Mancini F, Mahajan P, Guttesen AÁV, Onysk J, Scholtes I, Shenker N, Lee M, Seymour B. Enhanced behavioural and neural sensitivity to punishments in chronic pain and fatigue in rheumatoid arthritis. Brain 148(6), 2151–2162 (2025).

4. Yanagida T, Fujita K, Iwaki M. The demon hidden behind life's ultra-energy-efficient information processing – demonstrated by biological molecular motors. arXiv preprint arXiv:2510.27212 (2025).

5. Seymour B, Crook RJ, Chen ZS. Post-injury pain and behaviour: a control theory perspective. Nature Reviews Neuroscience 24(6), 378–392 (2023).

Immunology and Cell Biology

Masaru Ishii, MD/PhD

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Research Assistant	1
Visiting Scientist	2
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 1]. 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].

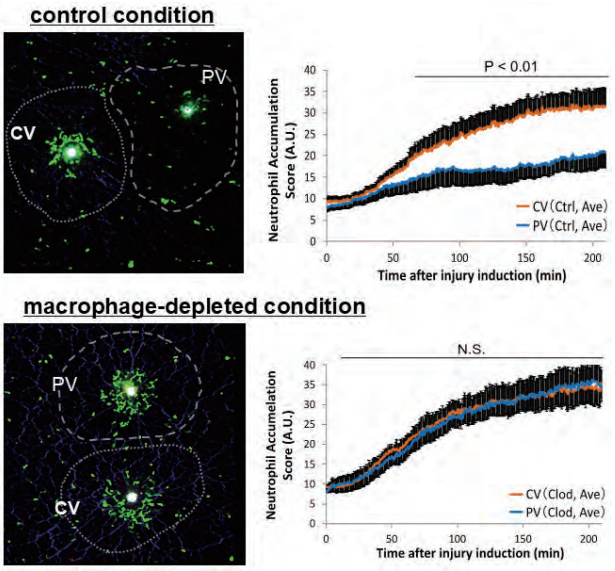

Figure 1.
Variability in inflammatory response to laser ablation in the liver. (Left) Inflammation induced by laser ablation. (Right) Significant inflammation (left) and mild inflammation (right) in response to the same stimulus.

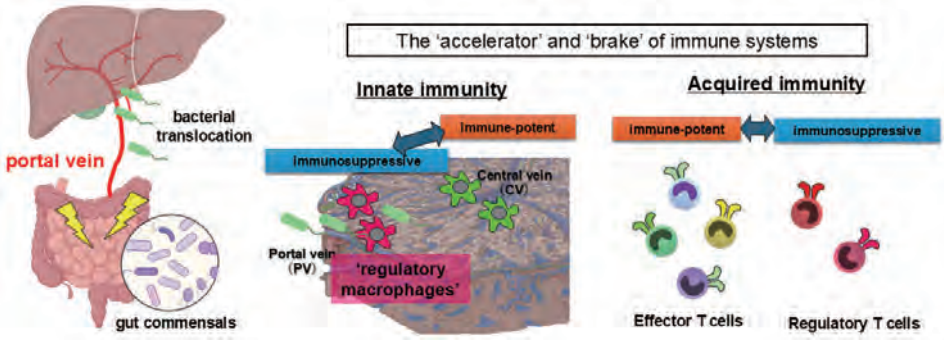

Figure 2.
The nature of immune tolerance in the liver and the significance of the "regulatory" innate immune system. (Left) The liver requires an immune tolerance mechanism because blood containing intestinal bacteria, nutrients, and other contaminants enters the liver via the portal vein from the intestines. (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.

Recent Publications

1. Kaneko T, Yari S, Kikuta J, Omatsu Y, Seno S, Kikuchi S, Sato K, Fujii K, Uchida Y, Sudo T, Hasegawa T, Furuta K, Guo Q, Ibrahim SH, Muraoka K, Okada Y, Kubota Y, Okuzaki D, Kobayashi Y, Kumanogoh A, Udagawa N, Nagasawa T, Penninger JM, Ishii M. The RANK/RANKL axis controls vascular dynamics in the bone marrow. Proceedings of the National Academy of Sciences of the United States of America 122(45), e2425366122 (2025).

2. Miyamoto Y, Kikuta J, Matsui T, Hasegawa T, Fujii K, Okuzaki D, Liu YC, 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).

3. Shimizu K, Kikuta J, Ohta Y, Uchida Y, Miyamoto Y, Morimoto A, Yari S, Sato T, Kamakura T, Oshima K, Imai R, Liu YC, 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. Nature Communications 14(1), 4417 (2023).

4. Taniguchi S, Matsui T, Kimura K, Funaki S, Miyamoto Y, Uchida Y, Sudo T, Kikuta J, Hara T, Motooka D, Liu YC, 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. Nature Communications 14(1), 143 (2023).

Chemical Imaging Techniques

Kazuya Kikuchi, PhD

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Controlling Intramolecular Rotation with Five-Membered Heterocycles Facilitates the Design of Highly Cell-Permeable Xanthene-Based Fluorogenic Probes

Fluorogenic probes are invaluable tools in biology and medicine, offering high sensitivity and background-free imaging. In recent years, significant advancements have been achieved in the development of fluorogenic probes, which have been successfully utilized across various fields including biosensor development, drug screening, protein function monitoring, and super-resolution imaging. Rhodamine spirolactone / spirolactam fluorophores have become the most promising fluorogenic probes based on the fluorescence switching by reversible spirolactone / spirolactam ring-opening and -closing reaction. However, achieving a high signal-to-noise ratio, target specificity, and robust cell permeability in wash-free imaging remains a significant challenge.

This study proposes a new design strategy for wash-free, fluorogenic ("OFF/ON") fluorophores engineered by incorporating five-membered heterocycles such as furan or thiophene at 9-position of the xanthene core. This increases conformational flexibility and facilitates intramolecular rotation in low-viscosity media, producing a dark OFF state. The fluorophores become a fluorescence ON state upon interaction with biomolecular targets by hindering intramolecular rotation (Figure 1a). This approach aims to avoid common spirolactone-based issues such as pH sensitivity, limited membrane permeability (zwitterionic forms at neutral pH), and aggregation/toxicity when hydrophobic ligands are attached.

We initially synthesized a series of xanthene-based fluorophores and evaluated their viscosity sensitivities. Some of the fluorophores including a thiophene-tetramethylrhodamine (Th-TMR) core showed large fluorogenic response in viscous media and stability under reducing conditions. Next, fluorogenic protein-labeling probes were synthesized by conjugating these fluorophores with ligands for self-labeling tags. The HaloTag probe (Th-TMR-Halo) showed strong fluorogenic activation with recombinant HaloTag by 147-fold. Live-cell imaging in mammalian cells expressing nuclear HaloTag yielded high fluorescence contrast in nuclei after labeling the fluorogenic probes (Figure 1b). Th-TMR-Halo showed the fluorescence signals within 10 min, with intracellular $t_{1/2}$ = 9.6 min. The fluorescence signal was 7.8-fold brighter than commercial TMR-Halo at the same concentration, attributed to improved cell membrane permeability. The Th-TMR fluorophores also showed fluorogenic response for other self-labeling protein tags such as SNAP-tag and PYP-tag.

Th-TMR-Halo exhibited insufficient photostability during long-term imaging, indicating a need for further improvement. Thus, we synthesized a sulfonic-acid-linked Th-TMR-Acid fluorophore, designated as Th-TMR-S-Acid, to enhance both photostability and water solubility. The corresponding HaloTag probe Th-TMR-S-Halo showed excellent fluorogenic response upon labeling to target protein and photostability under continuous illumination. This property enabled no-wash super-resolution imaging of tubulin network in both live and fixed cells. Using endothelial reticulum (ER)-expressing HaloTag and Th-TMR-S-Halo in HEK293T cells, stress-induced ER whorl formation was monitored in live cells. The time-lapse images visualized the dynamic formation of ER whorls, demonstrating a clear benefit of our probe for monitoring protein dynamics of target protein in live cell imaging.

To expand the applicability of our design, we developed BRD4- and epidermal growth factor receptor (EGFR)-targeting probes by

conjugating our fluorophores with non-covalent ligands such as JQ1 and gefitinib/erlotinib inhibitors. BRD4 involved in gene regulation through recognition of acetylated histones and is a promising therapeutic target in cancer and inflammatory diseases. On the other hand, EGFR overexpression is found in many cancer cells. The EGFR-targeting probe (Gefi-T) exhibited strong fluorescence in A431 cells with high levels of EGFR expression (Figure 1c). In contrast, a minimum fluorescence signal was observed in HEK293T cells with little expression of EGFR. These results demonstrate the effectiveness of the EGFR-targeting fluorogenic probes for detecting EGFR overexpression.

This work presents a versatile design strategy that leverages the controlled intramolecular rotation of furan/thiophene rings to create innovative OFF/ON fluorogenic probes, offering a robust platform for selective, wash-free live-cell imaging of diverse cellular targets. Overall, our approach expands the molecular toolkit for biomolecule detection in live cells and paves the way for future applications in biological and medical research.

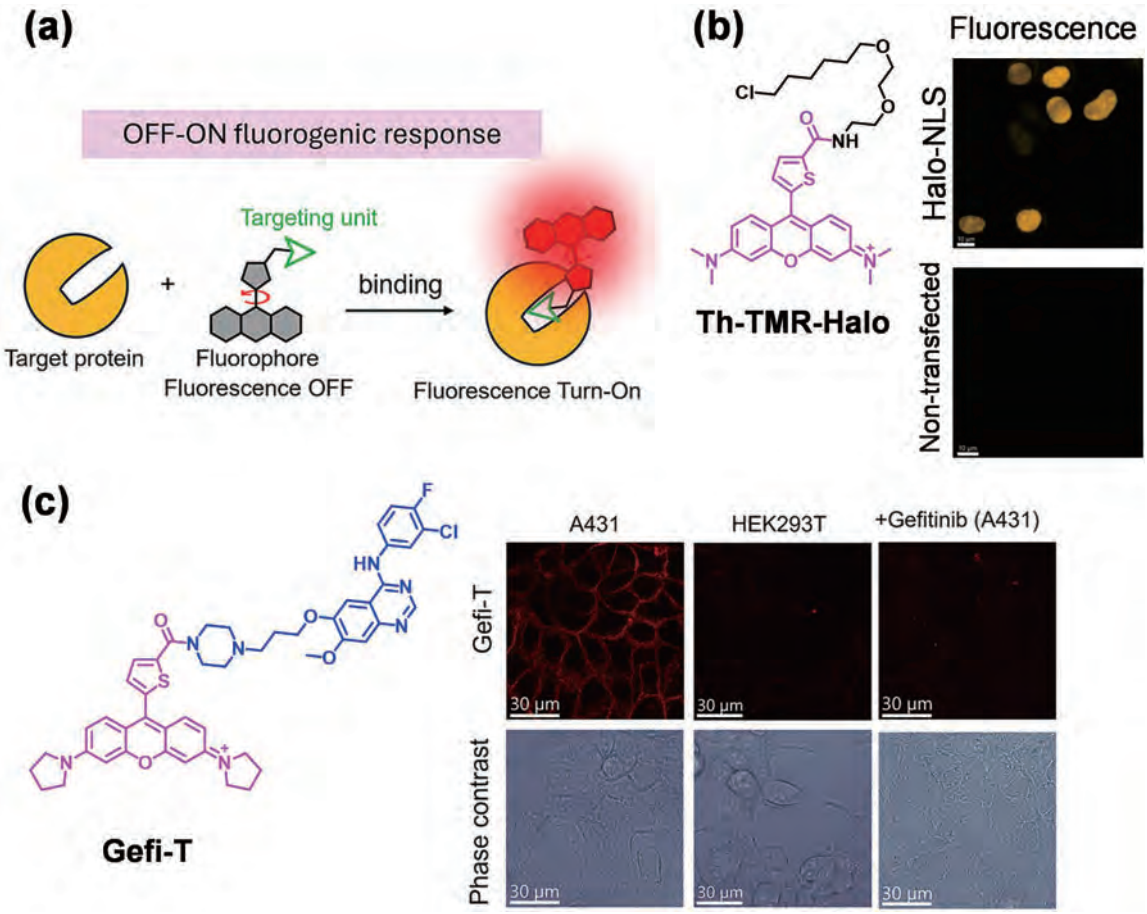

Figure.
(a) Schematic representation of the OFF–ON-based fluorogenic response through ring rotation restriction upon that occurs when the fluorophore attached to a protein-targeting unit interacts with the target protein. (b) Live-cell confocal fluorescence images of MCF7 cells expressing the Halo-NLS gene or non-transfected cells with 500 nM Th-TMR-Halo. Scale bar: 10 μm. (c) Live-cell imaging of endogenous EGFR with 5 μM Gefi-T on EGFR-overexpressing A431 and control HEK293T cells. Scale bar: 30 μm.

Recent Publications

1. Fukushima K, Yamamoto T, Kikuchi K. Kupffer cell capture-evading modifiable sub-20 nm lipid nanodisc-based 19F magnetic resonance imaging probes. Journal of the American Chemical Society 148, 12990–12997 (2026).

2. Reja SI, Hori Y, Takeda Y, Nishiura M, Minoshima M, Kikuchi K. Controlling intramolecular rotation with five-membered heterocycles facilitates the design of highly cell-permeable xanthene-based fluorogenic probes. Journal of the American Chemical Society 147, 47997–48012 (2025).

3. Farrag AMAS, Ota K, Yoshimura H, Takemoto M, Mitarai T, Kamikawa T, Abo M, Singh VP, Cui C, Zhou L, Ishidate F, Fujiwara T, Sato S, Hori Y, Ozawa T, Kikuchi K, Uesugi M. Live-cell monitoring and omics analysis of liquid–solid transitions of biomolecular condensates. Journal of the American Chemical Society 147, 37056–37064 (2025).

4. Wu Y, Minoshima M, Kikuchi K. Lipid bilayer-coated core–shell silica nanoparticles with enhanced clearance and biocompatibility for high-sensitivity 19F MRI. Analysis & Sensing 6, e202500178 (2025).

5. Verrier C, Louche A, Gauthier M, Ourri B, Ensenlaz S, Bordy M, Glenadel Q, Filopon D, Kikuchi K, Hasserodt J. Simplicity and reliability achieved in antimicrobial resistance testing through transformative design of a β-lactamase-responsive molecular probe. Analysis & Sensing 6, e202500160 (2025).

Immune Response Dynamics

Kazuhiro Suzuki, MD/PhD

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▶ Visiting Scientist	2
▶ 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 β2-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 β2-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 mouse 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 in both 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-mediated 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.

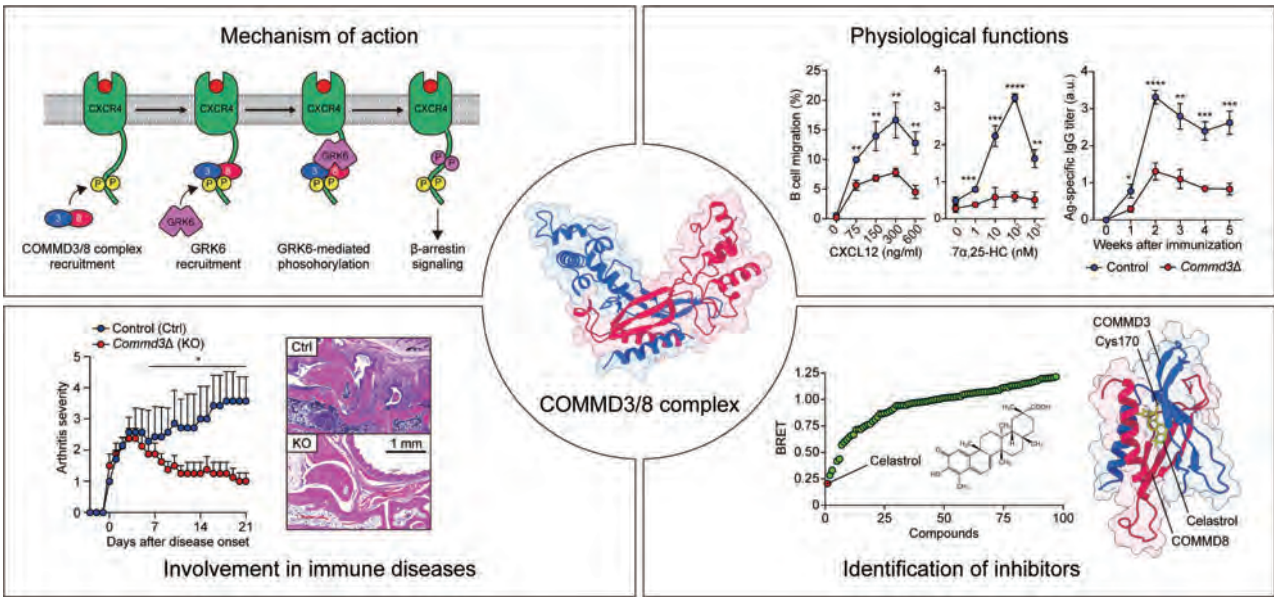


Figure.
Functional characterization of the COMMD3/8 complex.
Our study identified the COMMD3/8 complex as a positive regulator of chemoattractant receptors. Functional analyses revealed that it plays an important role in B cell migration and humoral immune responses. Furthermore, we demonstrated the involvement of the COMMD3/8 complex in the pathogenesis of autoimmune diseases and identified celastrol as a potent inhibitor of this complex.

Recent Publications

1. Ise W, Koike T, Shimada N, Yamamoto H, Tai Y, Shirai T, Kawakami R, Kuwabara M, Kawai C, Shida K, Inoue T, Hojo N, Ichiyama K, Sakaguchi S, Shiroguchi K, Suzuki K, Kurosaki T. KLF2 expression in IgG plasma cells at their induction site regulates the migration program. Journal of Experimental Medicine 222, e20241019 (2025).

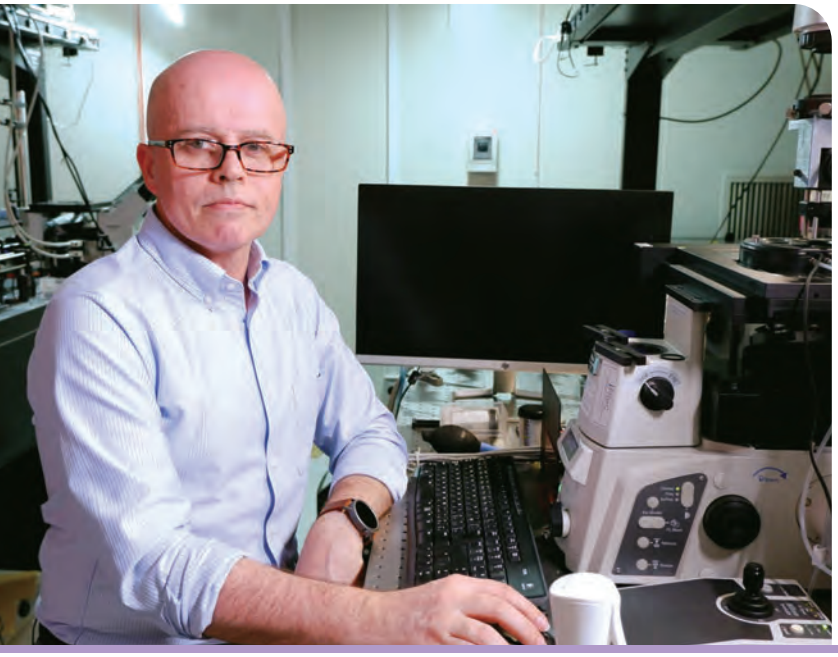
2. Shirai T, Nakai A, Ando E, Fujimoto J, Leach S, Arimori T, Higo D, van Eerden FJ, Tulyeu J, Liu YC, Okuzaki D, Murayama MA, Miyata H, Nunomura K, Lin B, Tani A, Kumanogoh A, Ikawa M, Wing JB, Standley DM, Takagi J, Suzuki K. Celastrol suppresses humoral immune responses and autoimmunity by targeting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

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

4. Suzuki K, Hayano Y, Nakai A, Furuta F, Noda M. Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes. Journal of Experimental Medicine 213, 2567–2574 (2016).

5. Nakai A, Hayano Y, Furuta F, Noda M, Suzuki K. Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors. Journal of Experimental Medicine 211, 2583–2598 (2014).

Biophotonics



Nicholas Isaac Smith, PhD

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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.

One of our projects dealt with lipid nanoparticles (LNPs), which have become one of the most consequential drug delivery devices recently, and their role in COVID-19 mRNA vaccines shows that getting biologically active cargo into cells efficiently is a key challenge that needs to be overcome for a wide range of applications. Typically less than 3.5% of RNA cargo escapes the endosome into the cytosol. Non-lamellar LLCNPs can potentially bypass this bottleneck by membrane fusion, but quantification of cellular uptake is essential. We solved this using Raman imaging, where the LNP uptake could be measured, independent of the fluorescent probes used in orthogonal fluorescence imaging and flow cytometry experiments. This was important because conclusions regarding uptake based only on labeled particles are subject to confounding effects where the label itself can modify uptake behavior. We performed Raman hyperspectral imaging of CHO cells incubated with each of the four LLCNP formulations for 6 hours at 532 nm excitation. Two components were diagnostic: one tracking general cellular content, and one tracking lipid-based molecules corresponding to the nanoparticles themselves. We then thresholded the score images to isolate cell regions and lipid-rich regions, and computed the ratio of integrated lipid signal to integrated cell signal for each condition (Figure 1 A, B). The results confirm the flow cytometry finding independently: non-lamellar LLCNPs, particularly cubosomes, accumulate in cells at substantially higher levels than liposomes. Because our measurement was label-free, it also demonstrated that the fluorescent tag used elsewhere in the study was not driving the observed uptake differences. We additionally verified via PCA that the uptake pattern in this case was essentially unchanged with or without serum, ruling out a protein corona artifact in CHO cells. The same approach can be used to determine how surface factors affect LNP or LNP-based vaccine uptake.

We also completed a project with our collaborators in Melbourne, which is focused on evaluating how micro- and nanoplastics (MNPs) interact with the immune system. MNPs are widely recognized as a global environmental and human health concern due to their ubiquity and persistence. A major problem in studying the downstream effects of MNP exposure is that most published work uses commercially manufactured polystyrene beads of uniform size and shape, which helps with experimental repeatability, but at the cost of being significantly different from real-world environmental MNPs in terms of chemistry, shape, texture, size, as well as the degree of homogeneity in the distributions. This makes it very difficult to extrapolate findings related to the effects of the particles in the studies to actual exposure scenarios. A key question was whether aging of polyethylene terephthalate (PET), polyamide 6 (Nylon), and polyacrylonitrile (PAN) resulted in chemical changes at the particle surface, or only physical fragmentation. We addressed this using

Raman microscopy, which is used in MNP research for polymer identification but can also report on oxidative surface modifications. We recorded Raman images of each polymer before and after aging with triplicate images per sample and multiple particles per image. The results showed that aging increased autofluorescence backgrounds substantially in PET and PAN, with a dome-shaped baseline dominating the PAN spectrum after treatment and nearly eclipsing the 2239 cm^{-1} nitrile band. Nylon showed a smaller but still measurable baseline elevation. Together with the LDIR, zeta potential, and autofluorescence data, this shows that such processing is important and results in significantly different chemistry, so that studies on the health effects of microplastics must take into account such environmental effects; claims of toxicity and immune activation should be considered in the context of how closely the experimental samples match real world particles. We are continuing to work on this important topic.

We also published findings on non-invasive discrimination of regulatory T cells, cryo-Raman and cryo-fluorescence imaging, and high-throughput Raman imaging. We continued to work with our collaborators towards quantifying lipid uptake and diffusion in a range of cellular and tissue targets, including human studies, and comprehensive elucidation of lipid nanoparticle uptake in mRNA vaccines in different types of cells.

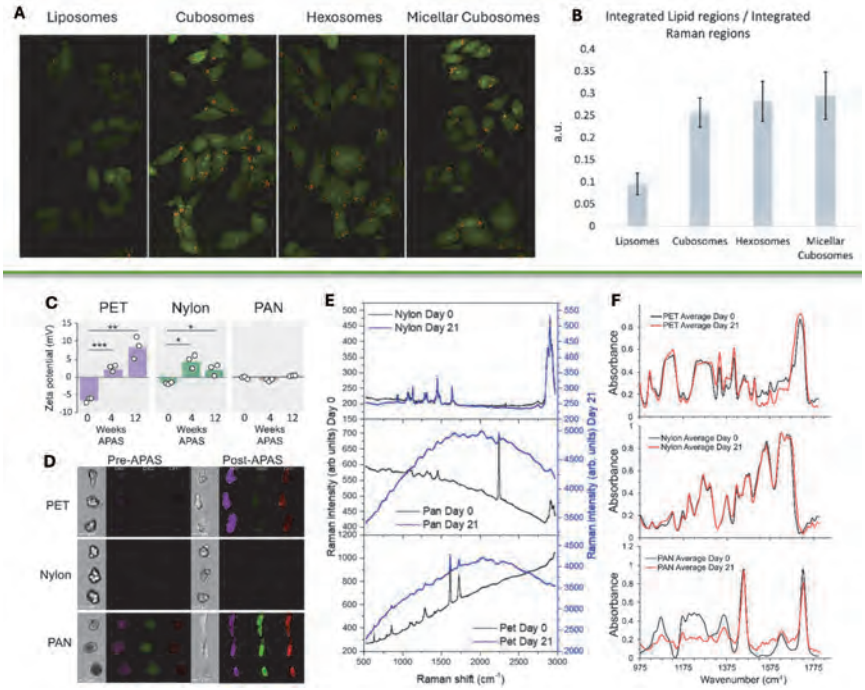

Figure.
Recent results using Raman microscopy, analysis of lipid uptake and microplastics. Starting from the top-left, MCR-ALS images generated from Raman microscopy compare the uptake of different lipid nanoparticles suitable for drug delivery at 6 h incubation. A) False color images of MCR-ALS components representing the cell (green) and lipid-rich regions (red). B) The lipid uptake was quantified by integrating the intensities from the lipid-rich regions and dividing by total cell area (see Experimental Section for details), showing the increase in lipid content for the non-lamellar lipid nanoparticles relative to liposomes. Panels C-F show the influence of aging on particle charge and spectral properties. (C) Zeta potential shows surface chemistry change induced by aging (APAS) of polyethylene terephthalate (PET), polyamide 6 (Nylon), and polyacrylonitrile (PAN) powdered plastics before, and after 4 and 12 weeks as measured by DLS. (D) Autofluorescence of plastics before and after 4 weeks of APAS measured by imaging flow cytometry. Ch07 excitation 405nm laser, emission filter 435-505nm. Ch02 excitation 488nm laser, emission filter 480-560nm. Ch11 excitation 405nm and 642nm laser, emission filter 642-745nm. (E) For comparison, average Raman spectra of PET, Nylon, and PAN particles at day 0 (black) or at day 21 (blue) of APAS. Raman intensity scales for day 0 samples are shown in black on the left-hand axis and Raman intensity scales for day 21 samples are shown in blue on the right-hand axis. Number of spectra included in the averages: Nylon day 0 n= 35344; Nylon day 21 n= 33488; PAN day 0 n=50072; PAN day 21 n=52551; PET day 0 n=34706; PET day 21 n=37403. (D) Average LDIR spectra of PET, Nylon, and PAN particles at day 0 (black) or at day 21 (red) of APAS..

Recent Publications

1. Yap SL, Dyett B, Hobro AJ, Nguyen H, Smith NI, Drummond CJ, Conn CE, Tran N. The internal nanostructure of lipid nanoparticles influences their diverse cellular uptake pathways. Small 21(40), 2500903 (2025).

2. Mizushima K, Kumamoto Y, Tamura S, Yamanaka M, Mochizuki K, Li M, Egoshi S, Dodo K, Harada Y, Smith NI, Sodeoka M, Tanaka H, Fujita K. Raman microscopy of cryofixed biological specimens for high resolution and high sensitivity chemical imaging. Science Advances 10(50), eadn0110 (2024).

3. 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).

4. Hobro AJ, Pavillon N, Koike K, Sugiyama T, Umakoshi T, Verma P, Fujita K, Smith NI. Imaging vs non imaging Raman spectroscopy for high throughput single cell phenotyping. Analytical Chemistry 96(18), 7047–7055 (2024).

5. Pavillon N, Lim EL, Tanaka A, Hori S, Sakaguchi S, Smith NI. Non invasive detection of regulatory T cells with Raman spectroscopy. Scientific Reports 14(1), 14025 (2024).

Systems Immunology

Daron M Standley, PhD

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Research Assistant	1
Visiting Scientist	6
Support Staff	1

Overview. Research in the Systems Immunology Lab aims to understand how immune responses are encoded and expressed at the molecular and system levels. For adaptive immune responses, we treat BCR and TCR repertoires as functional readouts of *in vivo* immune selection. The central question is not simply how to analyze repertoire data, but what these data reveal about antigen recognition, immune convergence, and disease-associated immune responses. To address these questions, we have developed computational approaches that infer antigen-binding properties from receptor sequence data and connect molecular-level features of receptors with donor-level phenotypes such as disease status and treatment response. In parallel, we have continued to support experimental studies through structural modeling and have begun expanding into experimental validation, including cryo-EM.

1. Analysis of BCR and TCR repertoires

Paratope-based representation of immune specificity.

A longstanding challenge in adaptive immunity is that individuals responding to the same antigen often show little or no overlap at the clonotype level, making shared immune responses across patients difficult to identify. We hypothesized that this apparent lack of overlap reflects the level at which similarity is measured, and that convergence is more readily detectable at the level of antigen-binding surfaces than lineage. To test this, we developed a paratope-based representation in which each receptor is described by its antigen-contacting regions (Davila A. et al 2022; Xu Z. et al 2024). Structural analyses indicate that antigen contacts are distributed rather evenly across multiple CDRs, supporting this representation. This allows each receptor to be treated as a functional unit whose similarity can be assessed using standard protein sequence analysis methods. This approach shifts the focus from lineage relationships to functional similarity and enables biologically meaningful comparisons across individuals.

Empirically, paratope-based clustering yields groups that closely reflect antigen and epitope specificity. In a controlled benchmark using diphtheria-tetanus-pertussis (DTP) vaccinated donors (Figure 1A), clustering based on paratope sequences was experimentally assessed (Saputri D. et al, 2023). FACS-based determination of B cell targets initially suggested cluster purity of only 82%; however, subsequent ELISA-based assessment showed the actual purity was 96% (Figure 1B). Furthermore, neutralizing antibodies clustered together (Figure 1C–E), indicating that paratope clusters group antibodies by epitope. We are now exploring whether these findings can support development of a simplified whooping cough vaccine candidate based on a single immunogenic pertussis toxin subunit, which could potentially reduce manufacturing complexity relative to multi-component formulations.

Building on these results, we have developed general purpose bioinformatics tools for clustering, searching, and classifying BCRs and TCRs based on their paratopes. These methods compare favorably to conventional approaches. For example, given the task of determining whether two antibodies target the same antigen and epitope, our paratope-based classifier exhibited a ROC AUC of 0.96, much higher than conventional clonotype-based classifiers (0.89).

2. From molecular features to donor-level phenotypes

Diagnostic modeling.

A long-term goal of the lab is to leverage molecular-level BCR/

TCR repertoire analysis for disease detection. Our first efforts focused on binary classification (healthy vs. disease) using publicly available data. This analysis clearly showed that paratope-derived features improved disease classification across infection, autoimmunity, and cancer compared with clonotype-based features, while revealing potential cancer-targeting T cells in the PBMCs of healthy donors (Xu, Z. et al, 2024). Building on this work, and incorporating a more scalable paratope embedding method, we developed a multi-disease classifier. In retrospective public-data benchmarks, this classifier achieved very high accuracy across 15 conditions using TCR information alone, although prospective multi-site validation will be essential to establish clinical robustness (Figure 2A). Encouragingly, our classifier exhibited favorable performance compared to Stanford University's Mal-ID disease classifier (Figure 2B). Such Diagnostic AI methods have the potential to transform disease screening by extracting high-dimensional, actionable information from a single blood test.

Stratification modeling.

Immunotherapy has revolutionized both oncology and autoimmunity treatment, but even the best interventions are effective only in a subset of patients. To address this gap, we examined prediction of treatment outcomes from repertoire data. In rheumatoid arthritis, we cleanly separated Rituximab responders and non-responders based on pre-treatment BCR repertoire data (Figure 3A); notably, these BCR features could almost entirely be attributed to anti-citrullinated protein antibodies (ACPAs), implying a solid scientific foundation for the features. We also examined TCR repertoires of HNSCC patients before combined PD-1/CTLA4 treatment and again separated responders from non-responders (Figure 3B). In this case, TCRs sharing paratopes with tumor-infiltrating lymphocytes (TILs) were the major driver of response prediction, again suggesting the features have a clear scientific foundation.

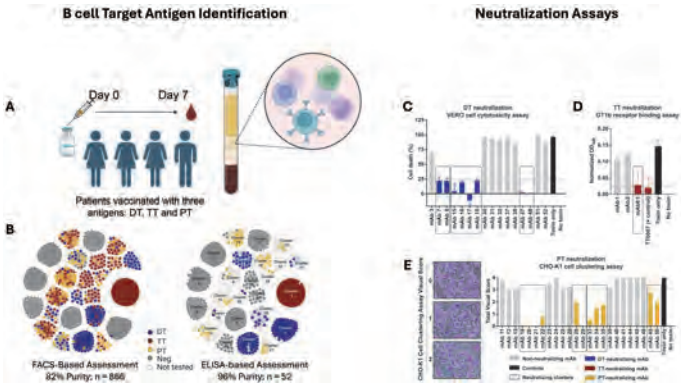

Figure 1.

Antigen purity of BCR paratope clusters using diphtheria tetanus pertussis (DTP) vaccinated donors.
A, Donors were vaccinated and their resulting BCR repertoires analyzed by paratope clustering. B, Initial FACS-based antigen and subsequent ELISA-based validation. Neutralization assays for diphtheria (C) tetanus (D) and pertussis (E).

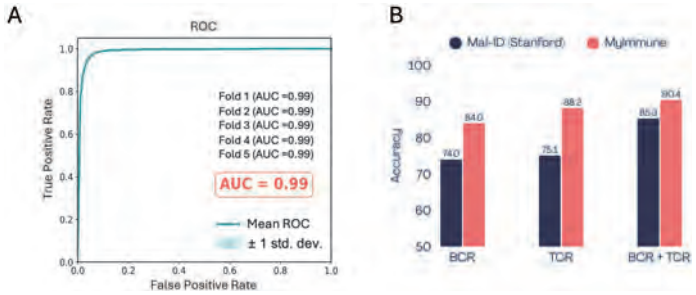

Figure 2.

Multi-disease prediction from paratope-based TCR features.
A, Analysis of 1450 donors covering 14 diseases in addition to a diverse healthy cohort. B, head-to-head comparison with Mal-ID on their 6-class (HIV, influenza, COVID-19, SLE, T1D and healthy) dataset.

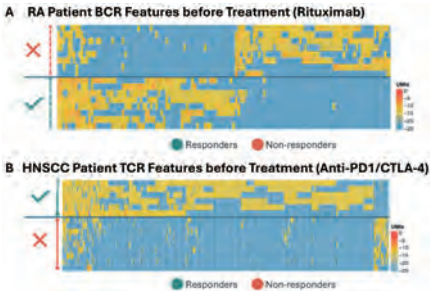

Figure 3.

Patient stratification by repertoire analysis.
A, Baseline analysis of RA patients treated with Rituximab. B, Baseline analysis of HNSCC patients undergoing treatment with PD-1/CTLA4.

Recent Publications

1. Xu Z, Ismanto HS, Saputri DS, Haruna S, Sun G, Wilamowski J, Teraguchi S, Sengupta A, Li S, Standley DM. Robust detection of infectious disease, autoimmunity, and cancer from the paratope networks of adaptive immune receptors. Briefings in Bioinformatics 25(5), bbae431 (2024).

2. Sakakibara S, Liu YC, Ishikawa M, et al. Clonal landscape of autoantibody secreting plasmablasts in COVID 19 patients. Life Science Alliance 7(12), e202402774 (2024).

3. Shirai T, Nakai A, Ando E, et al. Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex. Science Immunology 8(81), eadc9324 (2023).

4. Tanaka A, Maeda S, Nomura T, et al. Construction of a T cell receptor signaling range for spontaneous development of autoimmune disease. Journal of Experimental Medicine 220(2), e20220386 (2023).

5. Saputri DS, Ismanto HS, Nugraha DK, Xu Z, Horiguchi Y, Sakakibara S, Standley DM. Deciphering the antigen specificities of antibodies by clustering their complementarity determining region sequences. mSystems 8(6), e0072223 (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 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 guide precision medicine for complex immune disorders.

2. Projecting Human Genetics and Somatic Mutations into Single Cells.

We present the Osaka Atlas of Immune Cells (OASIS), a multi-layer, single-cell immune atlas built from 235 Japanese participants, including healthy donors and patients with COVID-19. We integrated single-cell transcriptomic and V(D)J profiling of more than 1.5 million high-quality peripheral blood mononuclear cells with host genome sequencing, plasma proteomics, and gut metagenomics to map how genetic, environmental, and somatic factors shape immune-cell states. We identified thousands of cell-type- and state-specific expression quantitative trait loci, showing that dense single-cell sampling can provide strong power even in a moderate-sized cohort and that non-European datasets capture regulatory effects not fully represented in European resources. We also linked HLA and genome-wide variants to T and B cell receptor repertoires, improved interpretation of disease-associated GWAS signals through colocalization, and revealed context-specific effects of polygenic risk on gene and protein expression. In addition, we projected somatic events, including mosaic chromosomal alterations, loss of Y chromosome, and mitochondrial DNA heteroplasmy, onto individual immune cells, uncovering mutation-associated immune phenotypes. Overall, OASIS provides a diverse, high-resolution resource for understanding state-dependent immune regulation and the molecular basis of complex human traits, supporting more equitable genomic discovery across populations and disease contexts.

3. Germline and Somatic Divergence of Human Y Chromosomes Impact Immune Profiles.

We investigated how germline and somatic variation on the Y chromosome contributes to male-specific genetic regulation and type 2 diabetes (T2D). We profiled Y-chromosome haplogroups and mosaic loss of the Y chromosome (LOY) in 122,683 East Asian males from BioBank Japan and 181,472 European males from the UK Biobank, and performed phenome-wide analyses across 90 traits. We found that Y-chromosome haplogroups showed population-specific associations with complex traits, including pleiotropic effects of the Japanese-specific haplogroup D on height and T2D. We also observed ancestry-dependent effects of LOY on T2D risk: LOY increased T2D risk in East Asians but was associated with reduced risk in Europeans. In East Asians, LOY particularly contributed to incident T2D among males with lower polygenic risk scores, suggesting that somatic Y-chromosome loss can explain disease susceptibility beyond inherited autosomal and sex-chromosome variation. By incorporating Y haplogroups and LOY status, we improved polygenic prediction of T2D risk. Finally, single-cell analyses revealed tissue- and cell-type-specific LOY accumulation, including enrichment in pancreatic β cells, where LOY may impair glucose metabolism. Overall, our study

highlights the clinical relevance of Y-chromosome variation for understanding, predicting, and managing T2D risk across populations.

4. Gene-Environmental Interaction Catalog.

We constructed a cross-population compendium of gene–environment interactions to clarify how environmental exposures modify genetic effects on human traits. We analyzed 440,210 individuals from European and Japanese populations, with replication in 539,794 individuals from diverse cohorts. By testing interactions between genome-wide variants and environmental factors, including age, sex, smoking, alcohol consumption, diet, and physical activity, we identified widespread gene–environment effects across biomarkers and diseases. We showed that these interactions contribute to missing heritability, reveal context-dependent trait relationships, and systematically influence polygenic prediction accuracy and its portability across populations. In Japanese cohorts, we observed prominent pleiotropic interactions at the East Asian-specific ALDH2 locus, highlighting the importance of non-European datasets for capturing population-specific biology. Cross-population analyses further demonstrated both shared and ancestry- or environment-specific interaction patterns. We decomposed the environmental contributors underlying these signals and found examples consistent with lifestyle effects and reverse causality from disease-related behavioral changes. We also projected genetic effects onto single-cell and multi-omics data, revealing age-dependent shifts in regulatory pathways, cell types, and sex-discordant effects in lipid metabolism relevant to drug development. Overall, our study provides a scalable framework and resource for interpreting dynamic genetic architecture, improving personalized risk prediction, and informing precision medicine across populations.

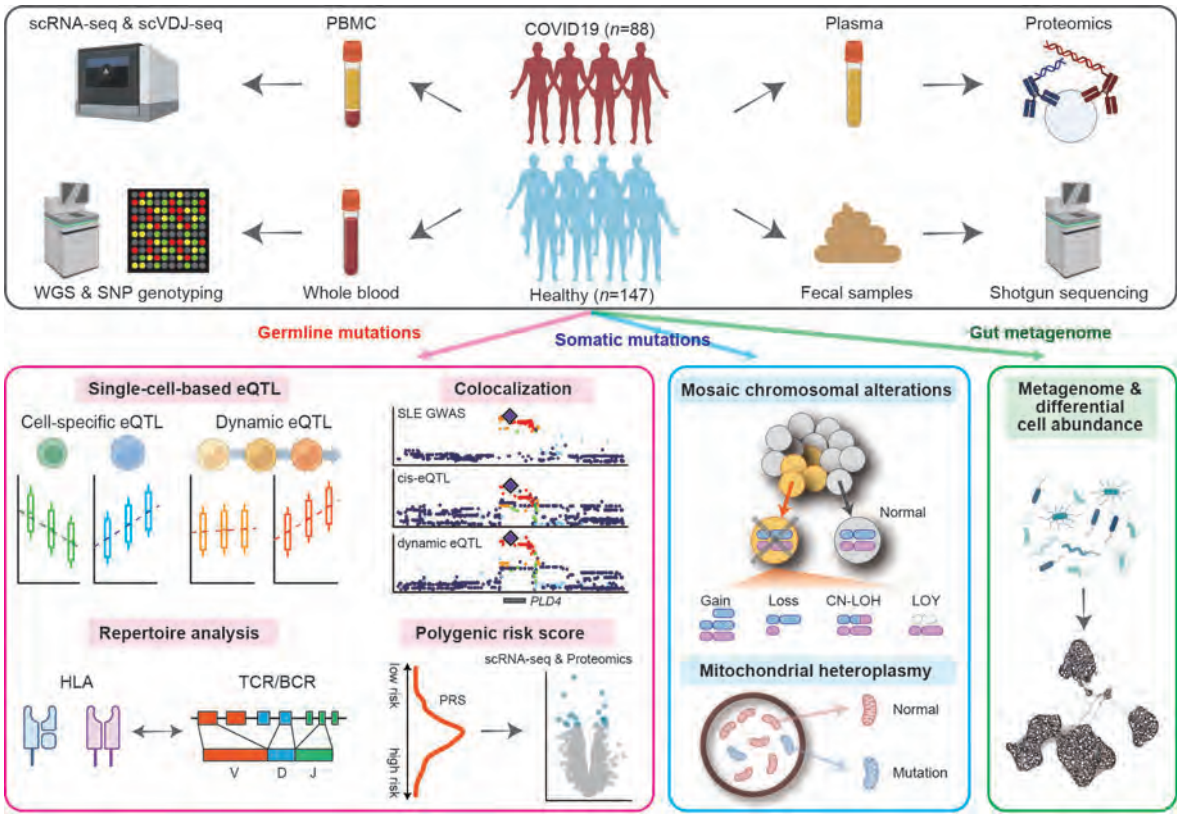

Figure.
Overview of Osaka Atlas of Immune Cells (OASIS).

Recent Publications

1. Sato G, Yamamoto Y, Sonehara K, et al. Genetic regulation across germline and somatic variation on the Y chromosome contributes to type 2 diabetes. Nature Medicine 32, 894–905 (2026).

2. Namba S, Sonehara K, Koyanagi YN, et al. A cross-population compendium of gene–environment interactions. Nature 651, 688–697 (2026).

3. Sonehara K, Watanabe R, Matsumura Y, et al. Whole-genome sequencing reveals rare and structural variants contributing to psoriasis and identifies CERCAM as a risk gene. Cell Genomics 19, 100978 (2025).

4. Edahiro R, Sato G, Naito T, et al. Deciphering state-dependent immune features from multi-layer omics data at single-cell resolution. Nature Genetics 57, 1905–1921 (2025).

5. Yamamoto Y, Shirai Y, Sonehara K, et al. Dissecting cross-population polygenic heterogeneity across respiratory and cardiometabolic diseases. Nature Communications 16, 3765 (2025).

Quantitative Immunology

▶ Associate Professor Diego Diez

Our group integrates 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 on 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 R2PVI, 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.

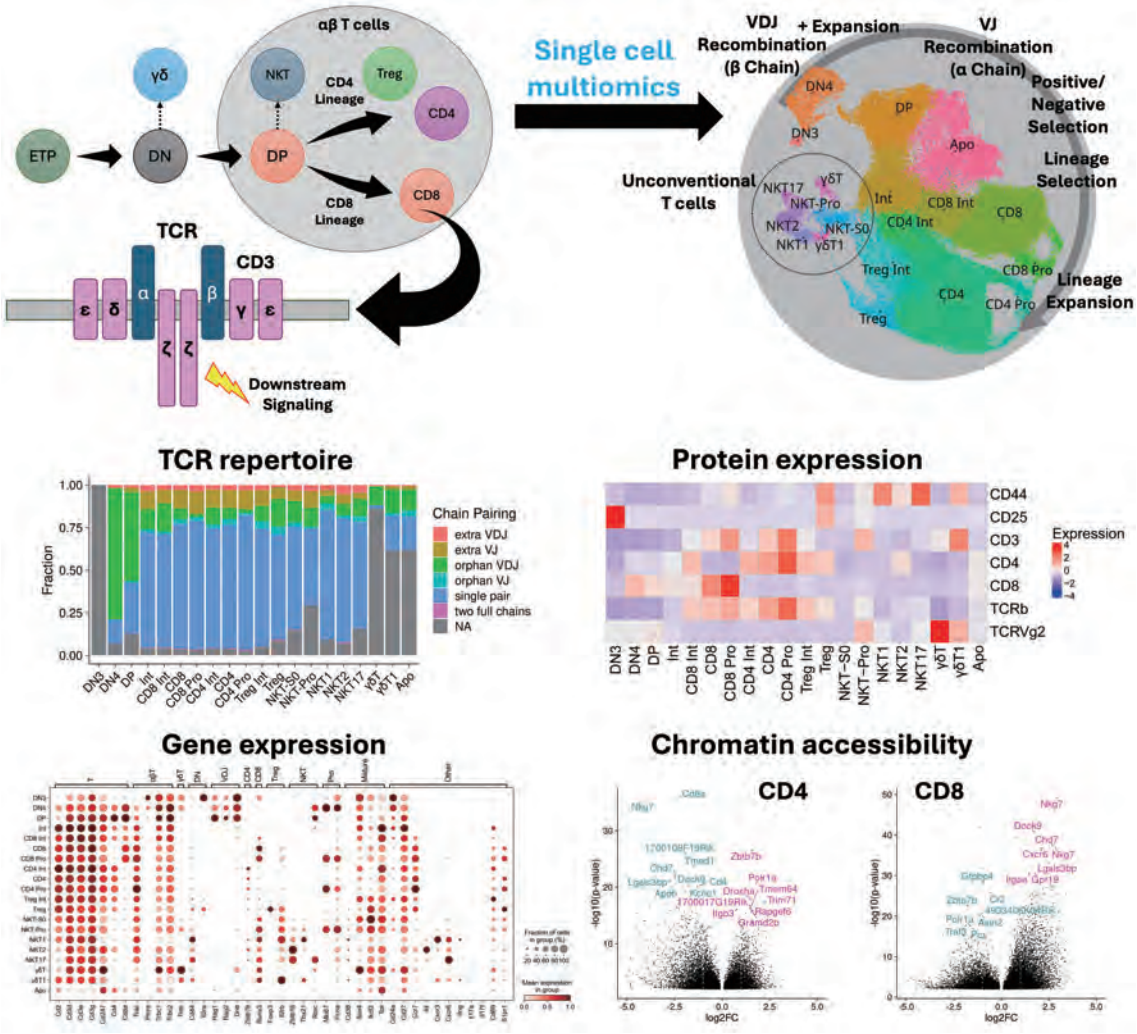

Figure.
Single cell genomics identifies differentiation pathways of developing thymocytes.

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. Scientific Reports 13, 11830 (2023).

3. Loza M, Teraguchi S, Standley DM, Diez D. Unbiased integration of single-cell transcriptome replicates. NAR Genomics and Bioinformatics 4, lqac022 (2022).

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, Diez D. A clustering-independent method for finding differentially expressed genes in single-cell transcriptome data. Nature Communications 11, 4318 (2020).


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Events & Outreach Activities

International Symposium on Advanced Immunology 2026
The 15th International Symposium of IFReC

This symposium was co-hosted by ©Senri Life Science Foundation and IFReC. World-leading scientists gathered at this two-day symposium to present lectures highlighting recent achievements in basic research in microbiology and immunology. On the first day, Professor Shimon Sakaguchi of IFReC, a 2025 Nobel Laureate, delivered a lecture. In addition to well-established scientists, promising early-career researchers also gave presentations, particularly for the second day of the symposium.

▶ **Date:** February 5-6, 2026

▶ **Venue :** Yuichi Yamamura Commemorative Life Hall, the 5th floor at the Senri Life Science Center, Osaka, Japan

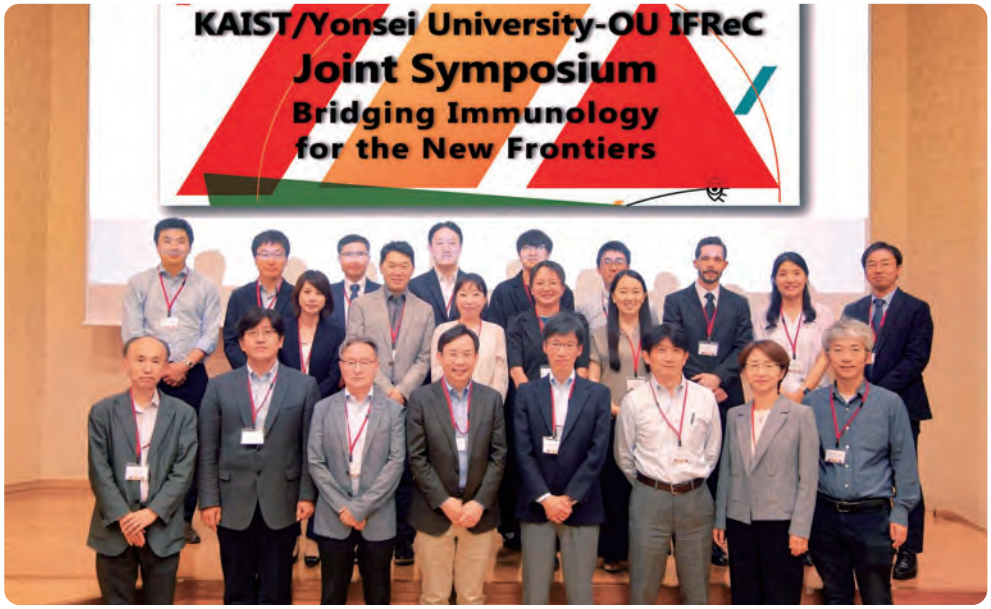
Feb. 5	
Tadamitsu Kishimoto (IFReC)	'Interleukin 6; from its discovery to clinical application Past, Present and Future'
James Di Santo (Institut Pasteur, France)	'A T cell-centric View of Human Innate Lymphoid Cell Differentiation'
Kenneth Murphy (Washington University in St. Louis, USA)	'Dendritic cell diversity in directing discrete immune modules'
Miriam Merad (Icahn School of Medicine at Mount Sinai, USA)	'Macrophages: "Master regulators of inflammation control"'
Diane Mathis (Harvard University, USA)	'Meningeal Treg control of brain health and degeneration'
Shimon Sakaguchi (IFReC)	'Treatment of immunological diseases by converting disease-mediating T cells into Tregs'
Feb. 6	
Christophe Benoist (Harvard University, USA)	'Immgen T'
Shunsuke Mori (IFReC)	'Discrimination of Self and Neoself Antigens by T Cells in Immune Homeostasis'
Kazuki Nagashima (Harvard University, USA)	'Mapping the T cell repertoire to a model system of the human gut microbiome'
Caterina Faliti (Emory University, USA)	'Mapping B Cell Tolerance Breakdown in Lymph Nodes of Lupus Patients'
Ryuya Edahiro (IFReC)	'Integrative projection of multi-layer omics data into the single-cell immune landscape'
Akiko Oguchi (RIKEN/ Kyoto University, Japan)	'Mapping RNA dynamics in immunity in single cells and space'
Hiutung Chu (University of California San Diego, USA)	'Inflammation shapes bacterial evolution and host immunity'
Fiona Powrie (The University of Oxford, UK)	'Gut Reactions: Immune regulatory pathways in the intestine'
Kiyoshi Takeda (IFReC)	'Identification of microbiota-derived metabolite and T cell subset implicated in the pathogenesis of Crohn's disease'

The first KAIST/ Yonsei University-OU IFReC Joint Symposium Bridging Immunology for the New Frontiers

▶ Date: May 16, 2025

▶ Venue : Taniguchi Memorial Hall, The University of Osaka

Speakers	
KAIST/ Yonsei University	**IFReC**
Sang-Jun Ha (Yonsei University)	Hisashi Arase
Jun Young Hong (Yonsei University)	Wataru Ise
You-Me Kim (KAIST)	Sujin Kang
Kihyuck Kwak (Yonsei University)	Yumi Matsuoka
Ho-Keun Kwon (Yonsei University)	Kazuyo Moro
Jeong Seok Lee (KAIST)	Kazuhiro Suzuki
Seung-Hyo Lee (KAIST)	Kiyoshi Takeda
Ji Eun Oh (KAIST)	Masahiro Yamamoto
Eui-Cheol Shin (KAIST)	Sho Yamasaki

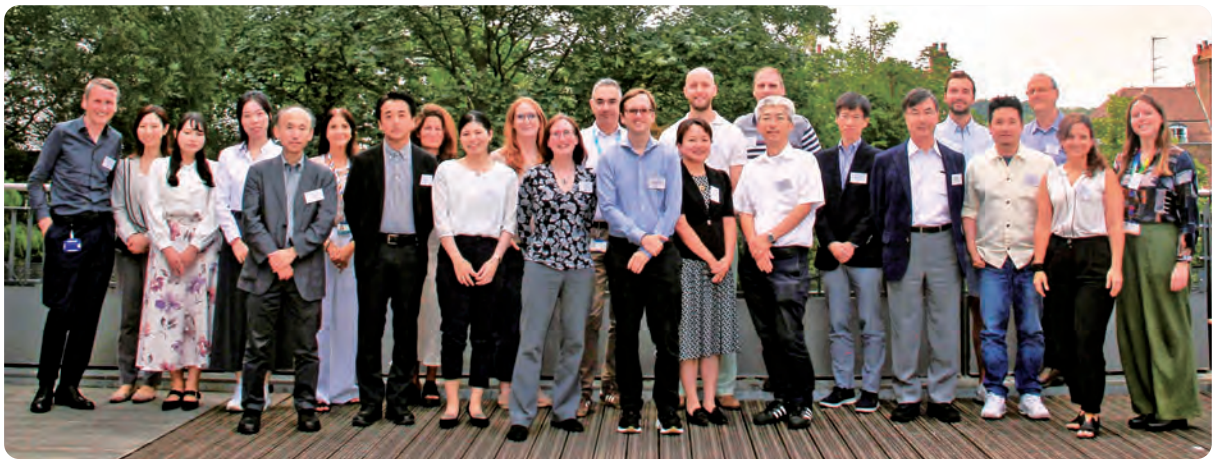


IFReC and IIT Co-host fourth Symposium on Immunology

- Date: June 20-22, 2025
- Venue : UCL Pears Building, London, UK

Speakers

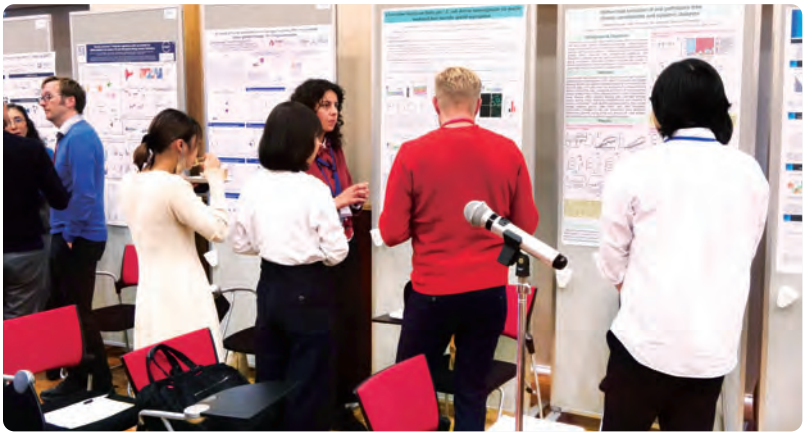
IIT, University College London	IFReC
Meryl Attrill	Hisashi Arase
Ursule Demael	Airi Ishibashi
Mariana Diniz	Yang Jing
George Finney	Ayumi Kuratani
Claudia Mauri	Yumi Matsuoka
Maddy Nousadeghi	Reo Morimoto
Peter Thomas	David Priest
Lucy Walker	Shimon Sakaguchi
Alan Zhuang	Barbora Salcman
	Kyioshi Takeda
	James Badger Wing
	Masahiro Yamamoto



ImmunoSensation² - IFReC Joint Workshop

▶ Date: December 8, 2025

▶ Venue : Taniguchi Memorial Hall, The University of Osaka



Speakers

ImmunoSensation², University of Bonn	IFReC
Zeinab Abdullah	Hisashi Arase
Rayk Behrendt	Wataru Ise
Gunther Hartmann	Masaru Ishii
Christian Kurts	Nobuhiko Kamada
Elvira Mass	Yumi Matsuoka
Katrin Paeschke	Kazuyo Moro
Anne-Katrin Pröbstel	Daron Standley
Andreas Schlitzer	Kazuhiro Suzuki
	Kiyoshi Takeda
	James Badger Wing
	Sho Yamasaki

The fourth ImmunoSensation² - IFReC International School on Advanced Immunology

The fourth International School on Advanced Immunology was held in Germany. Fifteen leading immunologists were invited as lecturers, and 50 exceptional participants were selected from 150 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: September 14-19, 2025
- Venue : Seehotel Maria Laach, Germany

Lecturer
Philipp Beckhove (Leibniz Institute for Immunotherapy, Germany)
Kaan Boztug (ImmunoSensation², University of Bonn, Germany)
Petter Brodin (Karolinska Institutet, Sweden)
Tomohiro Kurosaki (IFReC)
Alice Lepelley (Institute Imagine of Genetic Diseases, France)
Michael Lotze (University of Pittsburgh School of Medicine, USA)
Yumi Matsuoka (IFReC)
Anne-Katrin Pröbstel (ImmunoSensation², University of Bonn, Germany)
Jan Rehwinkel (University of Oxford, UK)
Georg Schett (University Hospital Erlangen, Germany)
Michal Schwartz (Weizmann Institute of Science, Israel)
Antigoni Triantafyllopoulou (Charite Berlin, Germany)
Roxane Tussiwand (ImmunoSensation², University of Bonn, Germany)
Dorothee Viemann (University Hospital Wurzburg, Germany)
Masahiro Yamamoto (IFReC)

Outreach Activities

In 2025, 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 14th WPI Science Symposium "NEW SCIENTIFIC EYES FOR CHANGING THE FUTURE"

- Date : November 15, 2025
- Venue : Tsukuba International Congress Center, Ibaraki
- Organizers : WPI-QUP and WPI institutions.

Life Science Seminar for high school students

- Date : August 8, 2025
- Venue : The University of Osaka and The Nippon Foundation Center for Infectious Diseases
- Speakers : Michiko Kodama (Graduate School of Medicine, Univ. Osaka)
  Kentaro Terada (Graduate School of Science, Univ. Osaka)

Exploring Research at WPI : Guide for Super Science High School students and educators

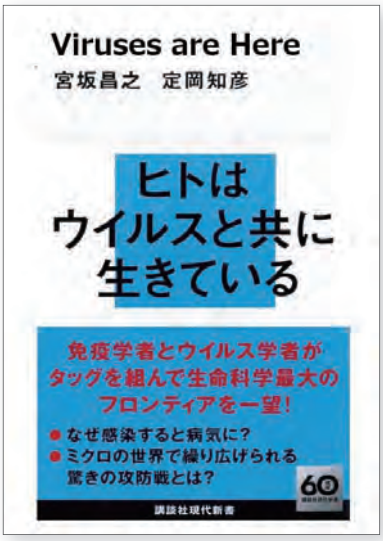
- July 19, 2025@Meijo University, Nagoya
- December 26, 2025@Okazaki Conference Center, Aichi

Science Café at the Nakanoshima Festival “Cell Death and Immunity”

- Date : November 30, 2025
- Venue : Lecture Hall A, The University of Osaka School of Medicine
- Speaker: Takaharu Sakuragi (Biochemistry & Immunology, IFReC)

Contribution to “Team Handai” project

In July 2020, The University of Osaka 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 2025, it had been publishing booklets introducing the University's research on infectious diseases to the general public until then. In addition, IFReC researchers have published books on infectious diseases for the general public.

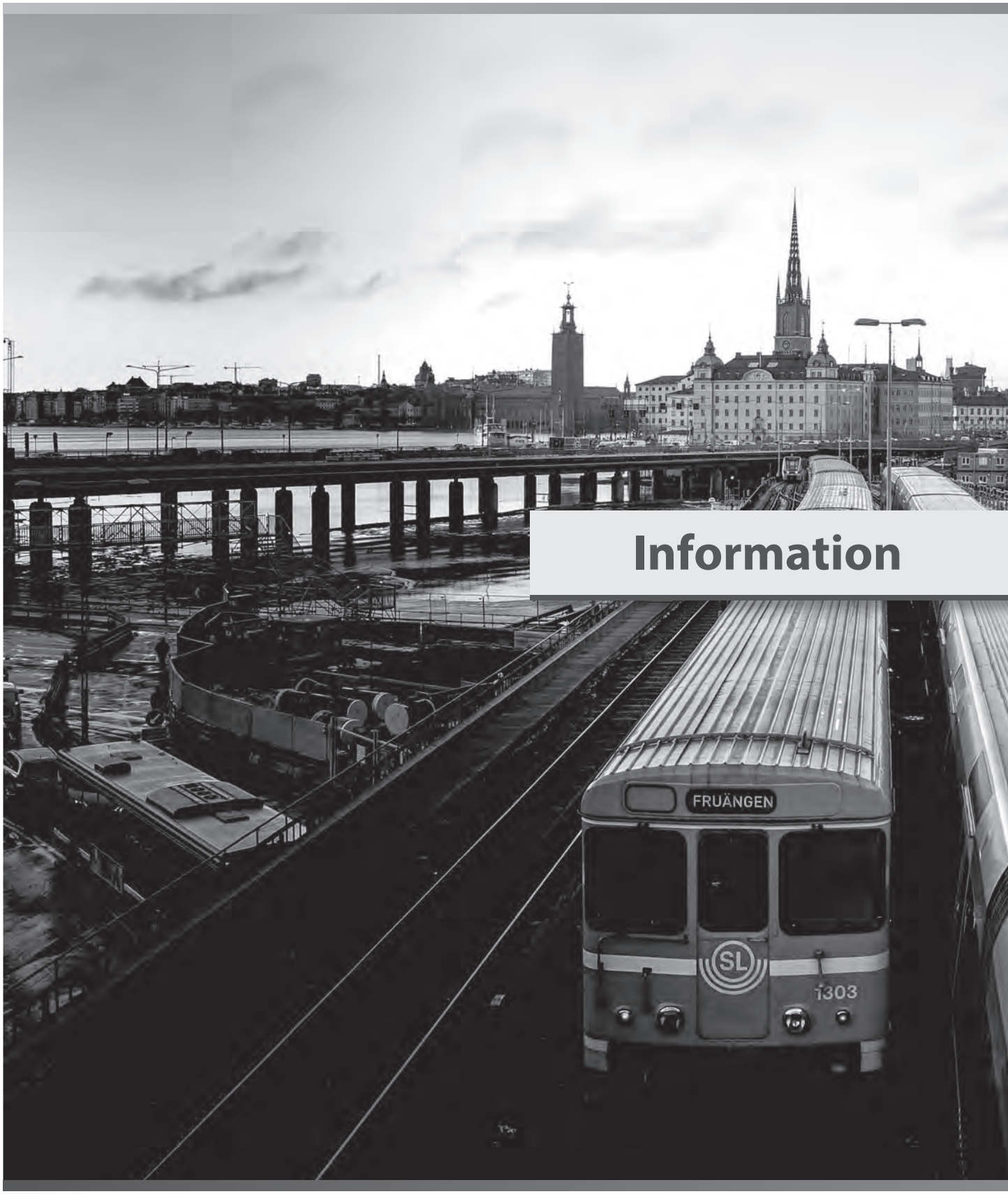


Japanese Language Class

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 Tajima. I always look forward to meeting you all every Tuesday and Thursday. This class mainly focuses on practicing speaking and listening skills. Each week, participants share various things about their daily lives, hobbies, hometowns and so on. We also have time for review, so even if you miss a class, you'll still be able to keep up. If you're interested in learning Japanese, please feel free to join us!



Information

Major Awards

Shimon Sakaguchi

The Nobel Prize for Physiology or Medicine 2025

"for the discoveries concerning peripheral immune tolerance"

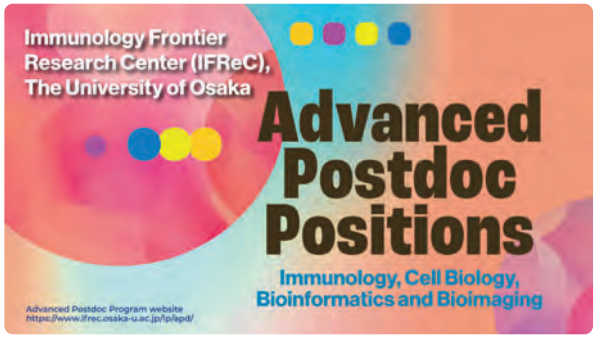
Shizuo Akira

The Japan Prize 2026

"Discovery of the nucleic acid sensing mechanism by the innate immune system"

Award	Awardee (s)
Highly Cited Researchers (HCR) 2025 by Clarivate ™	Nobuhiko Kamada, Shimon Sakaguchi
The Distinguished Fellow of American Association of Immunologists (AAI) 2025	Shimon Sakaguchi
The Ohtawara Toyoichi Prize 2025	Masahiro Yamamoto
The Mochida Memorial Award 2025	Hisashi Arase
Young Investigator Award of the Japanese Biochemical Society 2025	Takaharu Sakuragi

Advanced Postdoc Program at IFReC



IFReC has been recruiting post-doctoral 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

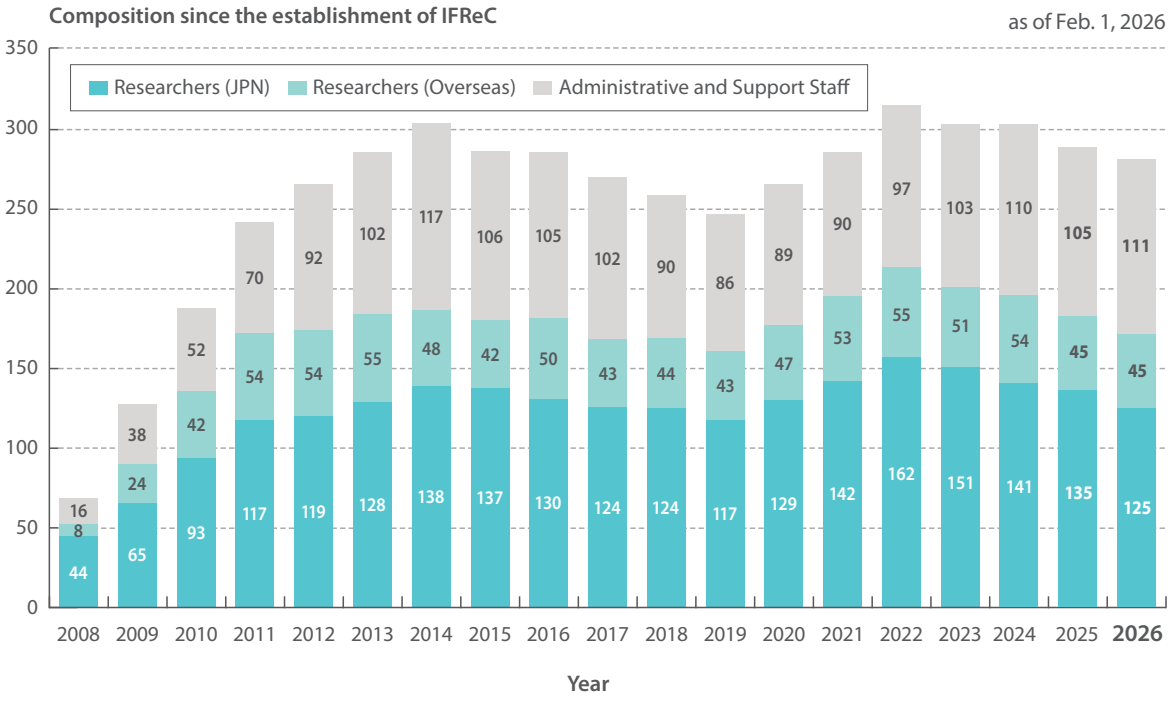
- Provision and maintenance of network infrastructure: LAN system and servers (web, mail, mailing lists, etc.)

Core Instrumentation Facility

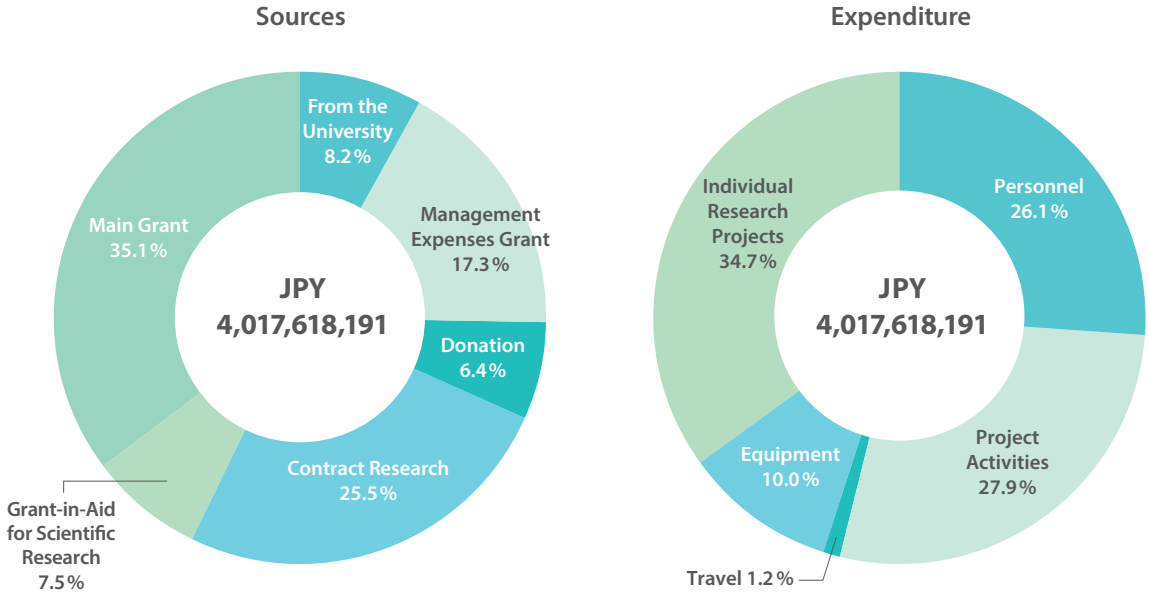
- Basic and advanced instruments
- In-house service
- DNA sequencing, cell sorting, electron microscopy, mass spectrometry and next-generation sequencing analysis
- Radio isotope facility

Composition & Finance

Composition



Finance



Selected Articles

CAR T or NK cells targeting mismatched HLA-DR molecules in acute myeloid leukemia after allogeneic hematopoietic stem cell transplant.

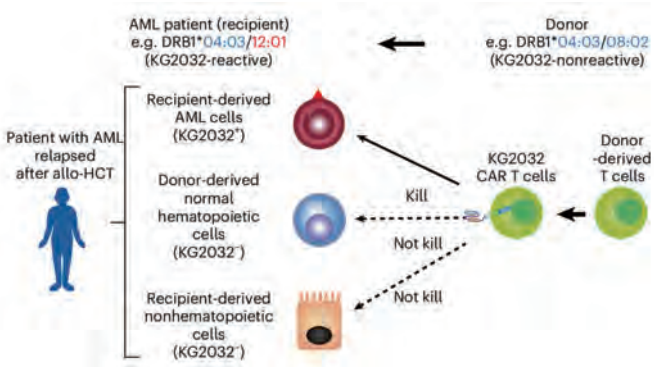
Ikeda S, Hasegawa K, Kogue Y, et al.

Nat Cancer. 2025 Apr;6(4):595-611.

doi: 10.1038/s43018-025-00934-1.

Chimeric antigen receptor (CAR) T cell therapy has markedly improved the survival of patients with relapsed or refractory B cell leukemia/lymphoma and those with multiple myeloma (MM). In addition, cord blood (CB)-derived natural killer (NK) cells transduced with a CD19 CAR were recently reported to be effective for B cell malignancies. However, acute myeloid leukemia (AML)-specific target antigens are difficult to identify.

The research group of Naoki Hosen demonstrated that HLA-DRB1 can serve as a leukemia-specific target of chimeric antigen receptor (CAR) T cells in patients with AML after allogeneic hematopoietic stem cell transplantation (allo-HCT).



RIFINs displayed on malaria-infected erythrocytes bind KIR2DL1 and KIR2DS1.

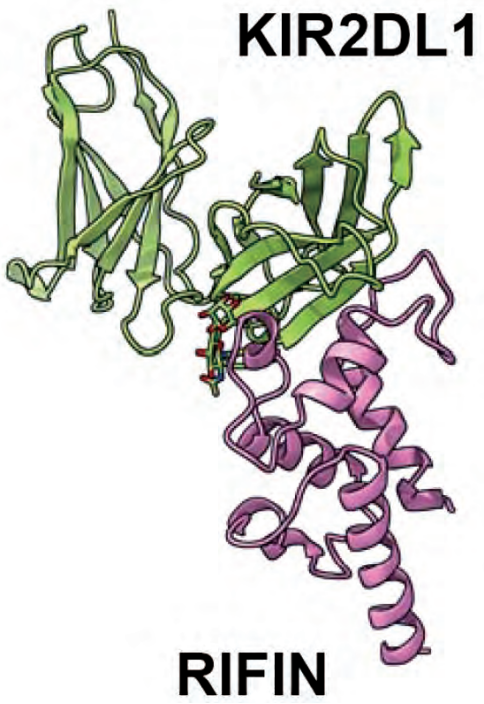
Sakoguchi A, Chamberlain SG, et al.

Nature. 2025 Jul;643(8074):1363-1371.

doi: 10.1038/s41586-025-09091-y.

It is known that Plasmodium falciparum (the parasite causing falciparum malaria) uses a protein called RIFIN on the surface of infected red blood cells to suppress immune cells, but the specific responses and attack mechanisms of human immune cells remained unclear.

A research group led by Hisashi Arase and Shiroh Iwanaga has clarified that while RIFIN stimulates inhibitory receptors on natural killer (NK) cells to suppress their function, NK cells also specifically attack parasite-infected red blood cells via activating receptors. Furthermore, the group discovered that RIFINs similar to those they identified exist in parasite strains worldwide, indicating that parasites and humans share common defense and attack mechanisms.



Transmission of maternal oral pathobionts to the infant gut predisposes offspring to exacerbated enteritis.

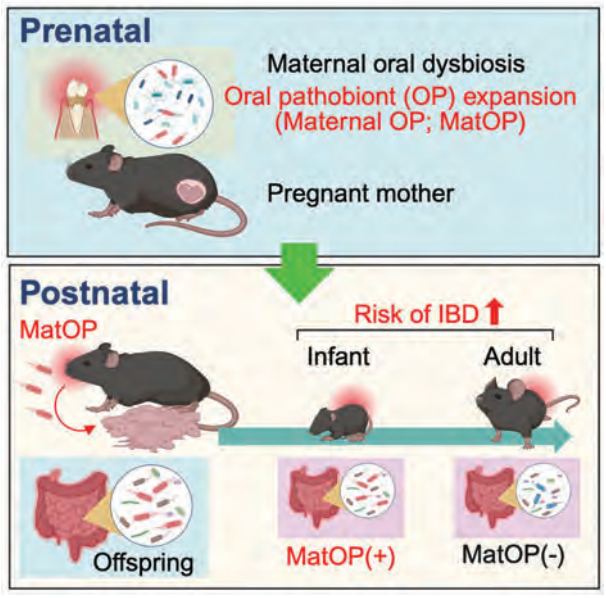
Haraguchi M, Kim Y, Watanabe N, et al.

Cell Rep. 2025 Jul;44(7):115974.

doi: 10.1016/j.celrep.2025.115974.

It has been shown that infants acquire microbes from various maternal sources (skin, oral cavity, intestine, vagina, etc.), and these microbes are among the earliest colonizers of the infant's gut. Therefore, disturbances in the mother's healthy microbial flora, particularly intestinal dysbiosis, may impact the composition of the child's gut microbiota and, consequently, their health. However, research on the effects of maternal microbes, beyond those from the intestine, on infant health and disease is limited.

A research group led by Hiroko Kitamoto and Nobuhiko Kamada demonstrated that maternal oral dysbiosis may have a lasting effect on children's health.



OTUD3 prevents UC by inhibiting microbiota-mediated STING activation.

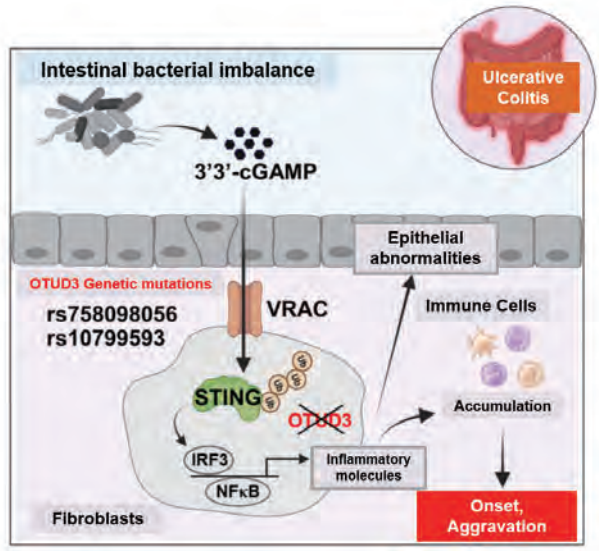
Li B, Sakaguchi T, Tani H, et al.

Sci Immunol. 2025 Jul;10(109):eadm6843.

doi: 10.1126/sciimmunol.adm6843.

Ulcerative colitis (UC) causes misery for millions worldwide. It affects the large intestine, causing pain, cramping, and frequent bowel movements with bloody diarrhea. Although some people go through periods when they feel well, the disease will suddenly flare up, causing another cycle of pain, diarrhea, and weight loss. There is currently no cure.

The research group of Hisako Kayama and Kiyoshi Takeda showed that OTU deubiquitinase 3 (OTUD3) suppresses pathologic activation of fibroblasts exposed to microbial cyclic GMP-AMP (3'3'-cGAMP) in the colon by deubiquitinating stimulator of interferon genes (STING).



Threonine phosphorylation of STAT1 safeguards gut epithelial integrity and restricts interferon-mediated cytotoxicity.

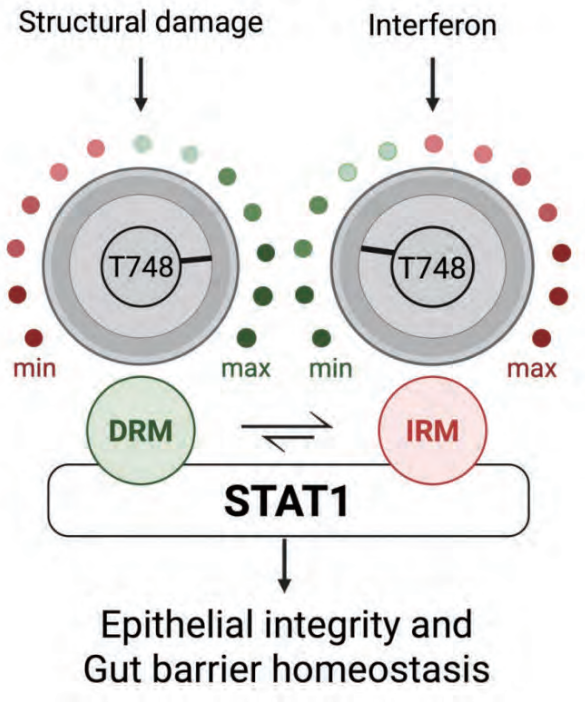
Metwally H, Elbrashy MM, Kayama H, et al.

Proc Natl Acad Sci U S A.
2025 Jul;122(30):e2511957122.

doi: 10.1073/pnas.2511957122.

Inflammation is a double-edged sword--essential for protecting the body and promoting healing, yet potentially harmful when left unchecked. A deeper understanding of how inflammatory responses are fine-tuned at the cellular level is critical for developing more precise and effective therapies.

For over than 30 years, STAT1 has been best known for its activation through tyrosine phosphorylation (Tyr701) in response to interferons, primarily mediating antiviral defense. The research group of Hozaifa Metwally and Tadamitsu Kishimoto identified a novel phosphorylation site -- threonine 748 (Thr748) -- on the immune signaling protein STAT1. These findings demonstrate that Thr748 phosphorylation acts independently of the canonical Tyr701 site to enhance epithelial resilience during inflammatory stress, such as colitis-induced tissue injury.



Multi-omics uncovers transcriptional programs of gut-resident memory CD4+ T cells in Crohn's disease.

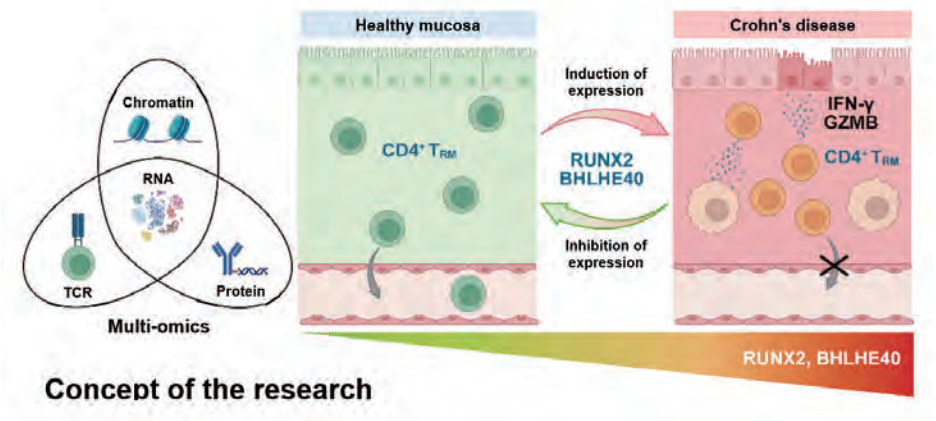
Arase M, Murakami M, Kihara T, et al.

J Exp Med. 2025 Nov;222(11):e20242106.

doi: 10.1084/jem.20242106.

Crohn's disease is an intractable disorder characterized by chronic inflammation in the digestive tract. Tissue-resident memory T cells (TRM), which persist in long-term in the intestinal mucosa, have been implicated in disease pathogenesis, but it has not been clear how these cells are induced.

The research group led by Mitsuru Arase, Mari Murakami, and Kiyoshi Takeda revealed that transcription factors RUNX2 and BHLHE40 play crucial roles in inducing T cells involved in Crohn's disease.



Generating functionally stable and antigen-specific Treg cells from effector T cells for cell therapy of inflammatory diseases.

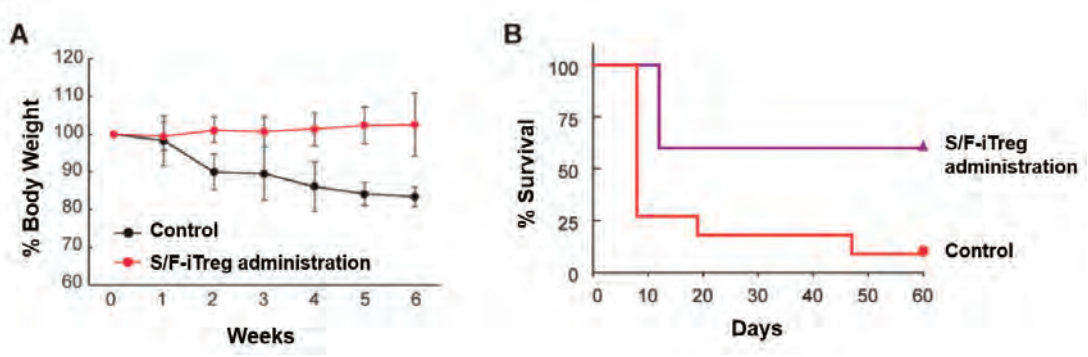
Mikami N, Kawakami R, Sugimoto A, et al.

Sci Transl Med. 2025 Oct;17(821):eadr6049.

doi: 10.1126/scitranslmed.adr6049.

Regulatory T cells (Tregs) are specialized T cells with immunosuppressive functions and are expected to play a key role in the treatment of autoimmune and inflammatory diseases. To achieve such therapies, the use of artificially induced Tregs (iTregs) has attracted considerable attention as a means to overcome the limitations of naturally occurring Tregs (nTregs). However, challenges remain regarding the stability and functionality of these cells.

A research group led by Norihisa Mikami and Shimon Sakaguchi has developed a novel method to artificially induce Tregs using disease-causing T cells as the starting material.



Comparative analysis of senolytic drugs reveals mitochondrial determinants of efficacy and resistance.

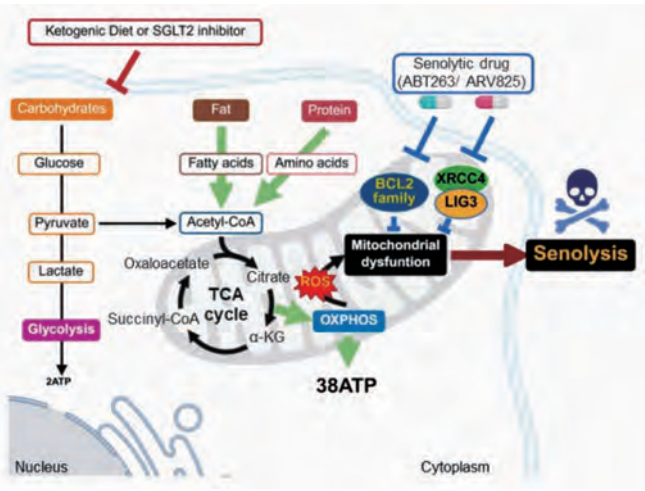
Wakita M, Ito K, Fujii K, et al.

Nat Aging. 2026 Jan;6(2):316-328.

doi: 10.1038/s43587-025-01057-z.

Senolytic drugs are a novel class of therapeutics that selectively eliminate so-called "zombie cells," which secrete inflammatory factors and promote aging in surrounding cells. These drugs have been developed with the goal of fundamentally treating age-related diseases, such as cancer, diabetes, and arteriosclerosis, as well as extending healthy lifespan. Over the past decade, more than 20 senolytic drug candidates have been reported; however, their mechanisms of action remain complex and diverse.

A research team led by Eiji Hara and Masahiro Wakita has systematically compared the efficacy of 21 senolytic drugs and identified a subpopulation of senolytic-resistant cells. The team demonstrates a mitochondrial basis for senolytic resistance and shows that metabolic interventions markedly enhance senescent cell clearance in vivo.



Publications

1. Abdelaal MR, Deng JR, McInerney MP, Ito E, Purcell AW, Yamasaki S, Villadangos JA, McWilliam HEG, Gherardin NA, Rossjohn J, Awad W. The antigen-presenting molecule MR1 binds host-generated riboflavin catabolites. Journal of Experimental Medicine 223, e20250711 (2026).
2. Abe H, Yamashita E, Okuzaki D, Ishii M. Granzyme A-producing type 1 innate lymphoid cells promote salivary secretion in the aged submandibular gland. Inflammation and Regeneration 46, 9 (2026).
3. Aoki S, Hori M, Zhang HJ, Tsujioka H, Yamashita T. Comparison of Spinal Cord Regeneration Capacity in Zebrafish and Medaka. Neurochemical Research 50, 153 (2025).
4. Arai M, Kawakami R, Nakamura Y, Naito Y, Motooka D, Sugimoto A, Kimoto T, Ohkura N, Mikami N, Sakaguchi S. Oral antigen exposure under costimulation blockade induces Treg cells to establish immune tolerance. Journal of Experimental Medicine 223, e20251635 (2025).
5. Arama E, Cosentino K, Czabotar PE, Gan BY, Hartland E, Jiang XJ, Kagan JC, Nagata S, Schroder K, Sun LM, Xu DC, Yuan JY. Towards a molecular and structural definition of cell death. Nature Structural & Molecular Biology 32, 1854-1858 (2025).
6. Arapa AM, Tallei TE, Idroes R, Fatimawali, Suoth EJ, Savitri M, Adam AA, Kolondam BJ, Yamada C, Ribeiro RIMD, Rani A, Park MN, Ophinni Y, Kim B. A multi-epitope pan-betacoronavirus vaccine construct predicted to induce broad-spectrum and durable immune responses: an immunoinformatics approach. Frontiers in Bioinformatics 6, 1784011 (2026).
7. Arase M, Murakami M, Kihara T, Kuwahara R, Toyota H, Sumitani N, Kinoshita N, Chen KY, Yokoi T, Motooka D, Okuzaki D, Zhao YH, Miyazaki H, Ogino T, Hirota S, Ikeuchi H, Takeda K. Multi-omics uncovers transcriptional programs of gut-resident memory $CD4^{+}$ T cells in Crohn's disease. Journal of Experimental Medicine 222, e20242106 (2025).
8. Ashikawa Y, Itokazu T, Yamashita T. Astrocyte regeneration via FGF8-DBX1 signalling facilitates recovery in neuromyelitis optica rats. Brain 148, 3763-3777 (2025).
9. Barnich N, Arthur JC, Buisson A, Campbell BJ, Carbonnel F, Chassaing B, Coombes BK, Denizot J, Dogan B, Faith J, Kamada N, Longman RS, Martinez-Medina M, O'Brien CL, Sartor RB, Zhang SY, Colombel JF, Simpson KW. Adherent-invasive Escherichia coli in Crohn's disease: the 25th anniversary. Gut 75, 411-424 (2026).
10. Bell A, Nakamura Y, Langley R, Hardcastle M, Katayama Y, Middleditch M. Staphylococcus pseudintermedius isolated from atopic dogs with pyoderma induces mast cell degranulation. New Zealand Veterinary Journal 74, 18-28 (2026).
11. Bhak Y, Raptis V, He YY, Nakanishi T, Macdonald-Dunlop E, Sagiya Y, Morisaki T, Matsuda K, Namkoong H, Kanai A, Suzuki Y, Oda Y, Kamatani Y, Namkoong H, Saiki R, Kimura A, Koike R, Ogawa S, Miyano S, Imoto S, Kanai T, Fukunaga K, Okada Y, Mälarstig A, Tenesa A. Identification and replication of sex-dimorphic protein quantitative trait loci across multiple ancestries and their associations with diseases. Scientific Reports 15, 31721 (2025).
12. Caro I, Western D, Namba S, et al. Proteogenomics in cerebrospinal fluid and plasma reveals new biological fingerprint of cerebral small vessel disease. Nature Aging 5, 2514-2531 (2025).
13. Cha S, Lee D, Kang J, Lee J, Kim S, Kang H, Park S, Kim M. Derivatizing immobilization methods for TEMPO radicals in metal-organic frameworks: Toward efficient aerobic oxidation and sequential reactions. Bulletin of The Korean Chemical Society 46, 468-480 (2025).
14. Chiba S, Kusuhara W, Ishikawa E, Yoritate M, Miura T, Maeda K, Takamura H, Matoba H, Yamasaki S, Hirai G. Linkage-Editing of β-Glucosylceramide and β-Glucosylcholesterol: Development of β-Selective C-Glucosylation and Potent Mincle Ligands. Journal of the American Chemical Society 148, 3316-3326 (2026).
15. De CK, Tsuda M, Zhu CD, Dehn S, Hinrichs H, Tsuji N, Jin H, Arase H, Tanaka S, List B. The Overlooked Stereoisomers of the Ionizable Lipid ALC315. Journal of the American Chemical Society 147, 28595-28600 (2025).
16. Dubey A, Yamashita E, Stangeland B, Abbas I, Fooksman D, Harris RA, Palmer GM, Koba WR, Zhang JH, Himes BT, Lu OR, Ho WS, Kuiper RV, Huffman D, Wu ZP, Uchida Y, Ishii M, Welch RL, Fiedler AF, Reynolds D, Hosainey SAM, Dobrenis K, Ye QG, Fisher K, Killian N, Stanley ER, Eskandar E, Behnan J. Brain tumors induce widespread disruption of calvarial bone and alteration of skull marrow immune landscape. Nature Neuroscience 28, 2231-2246 (2025).
17. Edahiro R, Sato G, Naito T, Shirai Y, et al. Deciphering state-dependent immune features from multi-layer omics data at single-cell resolution. Nature Genetics 57, 1905-1921 (2025).
18. Enomoto T, Takeda Y, Shirai Y, Hasegawa T, Zhao F, Lunding H, Pohl M, Edahiro R, Shichino S, Kawasaki T, Yoshimura H, Hara R, Amiya S, Yamamoto M, Nakatsubo D, Tanizaki S, Nakayama M, Noda Y, Niitsu T, Adachi Y, Tone M, Abe Y, Naito M, Masuhiro K, Naito Y, Shiroyama T, Miyake K, Koyama S, Fukushima K, Iwahori K, Hirata H, Nagatomo I, Nojima S, Yanagawa M, Inoue Y, Kumanogoh A. Serum C-C motif chemokine ligand 17 as a predictive biomarker for the progression of non-idiopathic pulmonary fibrosis interstitial lung disease. Respiratory Research 26, 157 (2025).
19. Fukumoto A, Yamanaka T, Yanaizu M, Nakamori M, Hama M, Yasumizu Y, Shiotsu K, Matsumura T, Nutter CA, Kubota T, Fujimura H, Kino Y, Swanson MS, Inoue K, Takahashi MP. Transcriptome alterations underlying metabolic dysfunction and liver disease in myotonic dystrophy type 1. Human Molecular Genetics 34, 1718-1732 (2025).
20. Fukushima K, Yamamoto T, Kikuchi K. Kupffer Cell Capture-Evading Modifiable Sub-20 nm Lipid Nanodisc-Based 19F Magnetic Resonance Imaging Probes. Journal of the American Chemical Society 148, 12990-12997 (2026).
21. Funakoshi K, Koike T, Ise W, Tai YK, Narazaki M, Kumanogoh A, Inoue T, Kurosaki T. TACI is required for the survival of short- and long-lived plasma cells. International Immunology 38, 197-206 (2026).
22. Gong W, et al. BATF2 is a glutamine-responsive tumour suppressor required for type-I interferon-dependent anti-tumour immunity. Nature Communications 17, 1271 (2025).
23. Harada A, Yasumizu Y, Harada T, Fumoto K, Sato A, Maehara N, Sada R, Matsumoto S, Nishina T, Takeda K, Morii E, Kayama H, Kikuchi A. Hypoxia-induced Wnt5a-secreting fibroblasts promote colon cancer progression. Nature Communications 16, 3653 (2025).
24. Haraguchi M, Kim Y, Watanabe N, Yamazaki K, Newman KL, Gillilland MG III, Guo YJ, Watanabe D, Bergin IL, Suzuki T, Motooka D, Sugihara K, Kitamoto S, Nagao-Kitamoto H, Kamada N. Transmission of maternal oral pathobionts to the infant gut predisposes offspring to exacerbated enteritis. Cell Reports 44, 115974 (2025).
25. Hashimoto K, Fukushima K, Matsumoto Y, Saito H, Funauchi A, Hamada N, Niitsu T, Abe Y, Yamauchi J, Nitta T, Motooka D, Nii T, Matsuki T, Tsujino K, Miki K, Kumanogoh A, Nakamura S, Kida H. Molecular epidemiological surveillance for non-tuberculous mycobacterial pulmonary disease: a single-center prospective cohort study. Microbiology Spectrum 13, e00436-25 (2025).
26. Hashimoto K, Fukushima K, Matsumoto Y, Saito H, Funauchi A, Hamada N, Yamauchi J, Nitta T, Motooka D, Nii T, Matsuki T, Tsujino K, Miki K, Komukai S, Kumanogoh A, Nakamura S, Kida H. Comparison of culture and culture-free methods for comprehensive identification of mycobacteria: a single-center prospective study. Journal of Clinical Microbiology 64, e01121-26 (2026).
27. Hayashi H, Tatsumi K, Katada H, et al. ROSE12, a novel anti-CTLA-4 FcγRs binding-enhanced antibody activated by extracellular adenosine triphosphate, shows tumor-selective regulatory T-cell depletion and antitumor efficacy without systemic immune activation. Journal for Immunotherapy of Cancer 14, e013397 (2026).
28. Higaki K, Aiba S, Shimoyama T, Omatsu Y, Nagasawa T. Universal fibroblasts across tissues can differentiate into niche cells for hematopoietic stem cells. Cell Reports 44, 115620 (2025).
29. Higasa K, Kamatani Y, Kawaguchi T, Kawaguchi S, Sakaue S, Yang TY, Okada Y, Momozawa Y, Yamaguchi I, Nelson D, Gravel S, Murakami Y, Yamada R, Matsuo K, Yamano Y, Kim C, Seo JS, Kubo M, Matsuda F. Whole-genome sequencing of 3135 individuals representing the genetic diversity of the Japanese population. Journal of Human Genetics 71, 223-230 (2026).

30 Higuchi S, Liu YF, Shimizu J, Ono C, Itoh Y, Nakai W, Jin H, Kishida K, Takayama K, Okamoto T, Murakami Y, Kinoshita T, Matsuura Y, Shioda T, Arase H. Evolutionary dynamics of heparan sulfate utilization by SARS-CoV-2. mBio 16, e00073-25 (2025).

31 Hirayama T, Konaka H, Kato Y, Shibahara T, Nishizawa C, Tsujimoto K, Park J, Itotagawa E, Jo T, Nishide M, Nishida S, Shima Y, Narazaki M, Aoki W, Ishii KJ, Takamatsu H, Kumanogoh A. Identification of Histone Deacetylase Inhibitor Targeting Type I Interferon and B Cell Abnormalities in Systemic Lupus Erythematosus. Arthritis & Rheumatology 78, 880-895 (2026).

32 Honcharuk V, Zainab A, Horimoto Y, Takemoto K, Diez D, Kawaoka S, Vandenbon A. DeepSpaceDB: a spatial transcriptomics atlas for interactive in-depth analysis of tissues and tissue microenvironments. Nucleic Acids Research 54, D1017-D1030 (2026).

33 Iida-Norita R, Miyata H, Ninomiya A, Emori C, Kamoshita M, Pan C, Wang HT, Ikawa M. Formation of a complex between TMEM217 and the sodium- proton exchanger SLC9C1 is crucial for mouse sperm motility and male fertility. Proceedings of the National Academy of Sciences of the USA 122, e2513924122 (2025).

34 Imamiya R, Ninomiya A, Kato H, Shinohara A, Horiguchi Y, Osada-Oka M. Bacterial proteins encapsulate in extracellular membrane vesicles from Escherichia coli-infected macrophages. Microbiology Resource Announcements 14, e00020-25 (2025).

35 Ishikawa E, Kosako H, Motooka D, Imasaka M, Watarai H, Ohmuraya M, Yamasaki S. Invariant TCR-triggered protein kinase D activation mediates NKT cell development. Journal of Experimental Medicine 222, e20250541 (2025).

36 Ishikawa T, Sonehara K, Sonoda K, Hayashi K, Kato K, Nagase S, Kusano K, Aiba T, Horie M, Ohno S, Okada Y, Makita N. A Genome-Wide Association Study Reveals Desmoglein-2 Predominance in Japanese Arrhythmogenic Cardiomyopathy. Journal of Arrhythmia 42, 702-713 (2026).

37 Ito E, Yamasaki S. Diversity and hallmarks of metabolites surveyed by MR1. Immunobiology 230, 153091 (2025).

38 Ito H, Ishikawa M, Matsumoto H, Ogura H, Okuzaki D, Oda J. Gene expression changes in lymphocytes and monocytes from patients with traumatic brain injury. Scientific Reports 16, 9150 (2026).

39 Ito H, Ishikawa M, Yoshimura J, Liu YC, Sakakibara S, Sugihara F, Matsumoto H, Hirata H, Ogura H, Oda J, Okuzaki D. Neutrophil gene expression in COVID-19 patients with acute respiratory distress syndrome. Frontiers In Immunology 16, 1620745 (2025).

40 Ito M, Ueda J, Yasuda S, Yabata I, Itagaki K, Banura N, Saito S. Time to Reperfusion Dictates Cardiac Function and Myocardial Strain in a 7-Tesla Magnetic Resonance Imaging Rat Model. Journal of Cardiovascular Development and Disease 13, 10 (2025).

41 Ito T, Kayama H. Roles of fibroblasts in the pathogenesis of inflammatory bowel diseases and IBD-associated fibrosis. International Immunology 37, 379–392 (2025).

42 Itoh T, Tanaka HN, Pareek M, Nagae M, Manya H, Ido A, Mishra SK, Kizuka Y. Enzymatic basis of branching and extension of O-Man glycans for keratan sulfate biosynthesis. Journal of Biological Chemistry 302, 111140 (2026).

43 Jo T, Tsujimoto K, Nakatani T, Nagira D, Muto Y, Hirayama T, Konaka H, Okada M, Takamatsu H, Kumanogoh A. The Ragulator complex and lysosomal calcium release are crucial for cell migration. Life Science Alliance 8, e202403015 (2025).

44 Kadariswantiningsih IN, Empitu MA, Santosa TI, Alimu Y. Antifungal resistance: Emerging mechanisms and implications (Review). Molecular Medicine Reports 32, 247 (2025).

45 Kanaoka K, Matsumoto K, Shiroyama T, et al. A Multicenter, Retrospective, Real-World Study of Atezolizumab Plus Chemotherapy and Pembrolizumab Plus Chemotherapy for Older Patients With NSCLC. JTO Clinical and Research Reports 6, 100891 (2025).

46 Kaneko T, Yari S, Kikuta J, Omatsu Y, Seno S, Kikuchi S, Sato K, Fujii K, Sudo T, Hasegawa T, Furuta K, Guo QQ, Ibrahim SH, Muraoka K, Okada Y, Kubota Y, Okuzaki D, Kobayashi Y, Kumanogoh A, Udagawa N, Nagasawa T, Penninger JM, Ishii M. The RANK/RANKL axis controls vascular dynamics in the bone marrow. Proceedings of the National Academy of Sciences of the USA 122, e2425366122 (2025).

47 Kanemoto G, Itokazu T, Nakanishi T, Furumiya T, Okada S, Yamashita T. Axonal sprouting from adjacent dorsal root ganglia following cervical dorsal root avulsion in mice. Neuroscience Research 220, 104971 (2025).

48 Katsuma K, Shimada K, Tonai S, Mashiko D, Iida-Norita R, Kaneda Y, Miyata H, Ikawa M. The absence of both RIBC1 and RIBC2 induces decreased sperm motility and litter size in male mice. Andrology 14, 545-554 (2026).

49 Kavian N, Kobiyama K, Ishii KJ, Coban C. Vaccine adjuvants as stand-alone immunoprophylaxis in strategies for 100-day rapid responses to future pandemics. International Immunology 38, 85-106 (2026).

50 Kawakami R, Sakaguchi S. Treg cells augment self-tolerance during infection. Nature Immunology 26, 650-652 (2025).

51 Kida S, Suga M, Yamaguchi Y, Ikeda S, Kogue Y, Kawamoto R, Shibata K, Tsutsumi K, Murakami H, Mizuta E, Mizutani Y, Hosen N. CAR T cells derived from a novel, high-affinity anti-CLL-1 monoclonal antibody exhibit a significant anti-AML effect. Cancer Immunology Immunotherapy 75, 92 (2026).

52 Kishi Y, Liu YC, Ishikawa M, Yamashita M, Matsumoto H, Ogura H, Sakakibara S, Okuzaki D. Mapping NK cell diversity in response to COVID-19 and mRNA vaccination. Scientific Reports 15, 37577 (2025).

53 Kock KH, Tan LM, Han KY, Ando Y, Jevapatarakul D, Chatterjee A, Lin QXX, Buyamin EV, Sonthalia R, Rajagopalan D, Tomofuji Y, Sankaran S, Park MS, Abe M, Chantaraamporn J, Furukawa S, Ghosh S, Inoue G, Kojima M, Kouno T, Lim J, Myouzen K, Nguantad S, Oh JM, Rayan NA, Sarkar S, Suzuki A, Thungsatianpun N, Venkatesh PN, Moody J, Nakano M, Chen ZY, Tian C, Zhang YT, Tong YH, Tan CTY, Tizazu AM, Loh M, Hwang YY, Ho RC, Larbi A, Ng TP, Won HH, Wright FA, Vilani AC, Park JE, Choi M, Liu BX, Maitra A, Pithukpakorn M, Suktitipat B, Ishigaki K, Okada Y, Yamamoto K, Carninci P, Chambers JC, Hon CC, Matangkasombut P, Charoensawan V, Majumder PP, Shin JW, Park WY, Prabhakar S. Asian diversity in human immune cells. Cell 188, 2288-2306 (2025).

54 Kogue Y, Ikeda S, Maehara Y, Kawamoto R, Suga M, Kida S, Shibata K, Tsutsumi K, Murakami H, Mizuta E, Mizutani Y, Yamaguchi Y, Okuzaki D, Hosen N. CAR NK cell production from human cord blood NK progenitor cells is enhanced by stimulation of the IL-15 receptor. Cancer Immunology Immunotherapy 74, 338 (2025).

55 Kohwi Y, Wong XR, Grange M, Sexton T, Richards HW, Kitagawa Y, Sakaguchi S, Liang YC, Chuong CM, Botchkarev VA, Taniuchi I, Reddy KL, Kohwi-Shigematsu T. Genome organization by SATB1 binding to base-unpairing regions (BURs) provides a scaffold for SATB1-regulated gene expression. eLife 14, RP105915 (2025).

56 Kumagai T, Andini TM, Sugiyama H, Standley DM, Park S. A variation in thiophene-extended nucleosides as microenvironment-sensitive fluorescent probes. Sensors and Actuators B-Chemical 455, 139639 (2026).

57 Kurashige M, Hino A, Muto K, Nagahama K, Yamamoto T, Nakata K, Ichii M, Fukushima K, Karube K, Nannya Y, Hosen N, Ogawa S, Morii E. Primary gastric EBV-positive cytotoxic-molecule-negative T-cell lymphoma with TET2 multihit mutations: a case report. Journal of Clinical and Experimental Hematopathology 66, 85-90 (2026).

58 Kurosaka S, Tanno H, Hirose M, Kamada W, Takayashiki R, Sone I, Sato Y, Watanabe T, Ishi S, Shoji M, Imai Y, Sato K, Ishii K, Hara H, Yamasaki S, Saijo S, Iwakura Y, Kawakami K, Kanno E. Contribution of CARD9 signaling to wound healing in skin promoted by topical administration of heat-killed Enterococcus faecalis strain KH2 and the involvement of Dectin-2. Frontiers In Immunology 16, 1550934 (2025).

59 Lammi V, Nakanishi T, et al. Genome-wide association study of long COVID. Nature Genetics 57, 1402–1417 (2025).

60 Lee J, Baek G, Kim Y, Park S, Kim M. A cytosine-silver incorporated metal-organic framework for efficient laccase-mimicking reactions. Dalton Transactions 55, 2817-2824 (2026).

61 Lee J, Wu HLA, Mannan AA, Nakamura Y, Amagai M, Irvine AD, Tanaka RJ. Toward the Next Generation of In Silico Modeling of Dynamic Host-Microbiota Interactions in the Skin. JID Innovations 5, 100385 (2025).

62 Li B, Sakaguchi T, Tani H, Ito T, Murakami M, Okumura R, Kobayashi M, Okuzaki D, Motooka D, Ikeuchi H, Ogino T, Mizushima T, Hirota S, Otake-Kasamoto Y, Kishikawa T, Nakamura S, Kobiyama K, Ishii KJ, Hashiguchi T, Kawai T, Kuroda E, Shinzaki S, Ise W, Kurosaki T, Kikuchi A, Tomofuji Y, Okada Y, Takeda K, Kayama H. OTUD3 prevents ulcerative colitis by inhibiting microbiota-mediated STING activation. Science Immunology 10, eadm6843 (2025).

63 Li SY, You WH, Martino MM. Cytokine Engineering Approaches for Regenerative Medicine. Advanced Therapeutics 8, e00103 (2025).

64 Lim EL, Qian YM, Sugihara F, Tanaka A, Sakaguchi S. Loss of PI3Kδ Activity Drives Autoimmune Colitis by Impairing Extrathymic Treg Differentiation. European Journal of Immunology 55, e70069 (2025).

65 Liu R, Lyu Q, Liu XY, Zou YR, Liu JX, Yu YJ, Zhou XY. Effects of gender differences and lifestyle factors on depression among Chinese children and adolescents. Bmc Psychology 14, 300 (2026).

66 Lu SL, Chen SY, Noda K, Li YJ, Tsai CY, Omori H, Kato Y, Zhang ZD, Chen BH, Tokuda K, Zheng TX, Wakita M, Hara E, Fukuda M, Wada Y, Morita E, Uzawa N, Murakami S, Noda T. Evidence that mitochondria in macrophages are destroyed by microautophagy. Nature Communications 16, 8123 (2025).

67 Lu TT, Umeshita S, Imanishi K, Wang YC, Liu YS, Nagae M, Senoo Y, Ikeda K, Fujita M, Kinoshita T, Murakami Y. ARV1 is a component of the enzyme initiating glycosylphosphatidylinositol biosynthesis. Journal of Biological Chemistry 301, 110236 (2025).

68 Lu Y, Seto Y, Hara Y, Takaya A, Uchida M, Kusuya Y, Ishibashi M, Nakamura Y, Takahashi H. Comparative genomics of Nocardia tsunamiensis IFM 10818, a new source of the antibacterial macrolide nargenicin A1. Microbiology Spectrum 13, e01220-25 (2025).

69 Mashiko D, Tonai S, Ikawa M. ADAM5 is required for sperm-zona pellucida binding and sperm oviduct migration. Biology of Reproduction 114, 1091-1100 (2026).

70 Mashiko D, Tonai S, Miyata H, Matzuk MM, Ikawa M. SLC35G3 is a UDP-N-acetylglucosamine transporter for sperm glycoprotein formation and underpins male fertility in mice. eLife 14, RP107494 (2025).

71 Matsuda M, Fujiwara Y, Yonezawa F, Matsuo K, Ishizu E, Shimora H, Shimizu S, Kitatani K, Kaibori Y, Yamagishi N, Yashiro T, Moro K, Kawakami R, Mikami N, Sakaguchi S, Nabe T. Cyclin-dependent kinase (CDK) 8 and its paralog CDK19 develop group 2 innate lymphoid cell-related lung fibrosis by activating STAT5. Journal of Immunology 214, 3238-3249 (2025).

72 Matsumaru T, Okubo K, Takayama J, Hirano Y, Huo YR, Toguchi S, Yoshida K, Fujii A, Suzuki T, Lin CC, Dohmae N, Yamasaki S, Fujimoto Y. Live-Cell Imaging Analysis of the Intracellular Behavior of the C-Type Lectin Receptor Mincle and Its Ligand Using Newly Developed Fluorescence-Labeled Molecular Probes Based on Trehalose Diester. ACS Chemical Biology 21, 519-526 (2026).

73 Matsumoto K, Naito Y, Shiroyama T, Tamiya M, Nishino K, Tamiya A, Okishio K, Kinehara Y, Kuge T, Mori M, Satoh S, Suzuki H, Tetsumoto S, Niki T, Suga Y, Osa A, Minami T, Koyama S, Takeda Y, Takakura N, Kumanogoh A. Impact of Sequential Ramucirumab Plus Docetaxel After PD-1 Inhibitors on Anti-PD-1 Antibody-Bound T-Cell Dynamics and Clinical Outcomes. Cancer Science 117, 929-942 (2026).

74 Matsumoto K, Noda Y, Hachiya K, Muramatsu F, Okamoto N, Jia WZ, Shiroyama T, Mori M, Tamiya M, Kinehara Y, Tamiya A, Shimizu S, Suzuki H, Ueno K, Niki T, Tetsumoto S, Morimura O, Osa A, Minami T, Nojima S, Takeda Y, Shintani Y, Kumanogoh A, Takakura N. Single-cell spatial analysis identifies ID1-high endothelial cells in tertiary lymphoid structures as predictors of durable response to immunotherapy in non-small cell lung cancer. Cancer Cell International 26, 65 (2026).

75 Matsuo-Dapaah J, Alshaweesh J, Lee MSJ, Hayashi T, Dash R, Kuroda M, Tainaka K, Ozawa M, Kuratani A, Yamamoto M, Liu KW, Fukui R, Miyake K, Kobiyama K, Rénia L, Ishii KJ, Coban C. IFNγ-inducible Gbp4 and Irgb6 contribute to experimental cerebral malaria pathology in the olfactory bulb. mBio 16, e01249-25 (2025).

76 Matsuura R, Punyawatthananukool S, Kawakami R, Mikami N, Sakaguchi S, Narumiya S. Prostaglandin E2-EP2/EP4 signaling induces the tumor- infiltrating Treg phenotype for tumor growth. Proceedings of the National Academy of Sciences of the USA 122, e2424251122 (2025).

77 Matsuura T, Abe M, Harada Y, Kido M, Nagahara H, Kodama Y, Ueda Y, Hara E, Niioka H, Matsumoto T. Selective identification of polyploid hepatocellular carcinomas with poor prognosis by artificial intelligence-based pathological image recognition. Communications Medicine 5, 270 (2025).

78 Mikami N, Kawakami R, Sugimoto A, Arai M, Sakaguchi S. Generating functionally stable and antigen-specific Treg cells from effector T cells for cell therapy of inflammatory diseases. Science Translational Medicine 17, eadr6049 (2025).

79 Mikami T, Kato I, Llamas-Covarrubias MA, Hiramatsu H, Uchihara Y, Mitsuyoshi T, Kitawaki T, Saida S, Umeda K, Ogawa S, Takaori-Kondo A, Wing JB, Takita J. CAR-T cells with the CD38-CD73-Tim-3-HLA-DR$^+$ phenotype predict the efficacy of tisagenlecleucel as a treatment for B cell precursor ALL. Cell Reports Medicine 7, 102576 (2026).

80 Mikami T, Kato I, Nishimura A, Eguchi-Ishimae M, Kamitori T, Tasaka K, Kubota H, Isobe T, Uchihara Y, Namikawa Y, Hamada S, Tsujimoto S, Inoue S, Hamabata T, Izawa K, Miyamura T, Tomizawa D, Imamura T, Toyoda H, Eguchi M, Goto H, Ogawa S, Takagi M, Wing JB, Takita J. Multi-omics analysis identifies an M-MDSC-like immunosuppressive phenotype in lineage-switched AML with KMT2A rearrangement. Nature Communications 16, 7955 (2025).

81 Miyamoto AT, Kumanogoh A, Nishide M. Current Overview of Multi-omics Analyses in Microscopic Polyangiitis and Granulomatosis with Polyangiitis. Internal Medicine 65, 226-232 (2026).

82 Miyazaki A, Matsumoto K, Tamiya M, Komuta K, Kanaoka K, Kuge T, Shiroyama T, Tsukaguchi A, Tamiya A, Yamauchi K, Suzuki H, Mihashi Y, Mori M, Moritomo K, Kinehara Y, Yoneda M, Morimura O, Azuma K, Tanaka S, Niki T, Osa A, Takeda Y, Kumanogoh A. Clinical Outcomes of First-Line Pembrolizumab Monotherapy in Advanced NSCLC With PD-L1 Tumor Proportion Score of 1% to 49%: A Retrospective Multicenter Study. Jto Clinical and Research Reports 7, 100953 (2026).

83 Mizuno Y, Matsushita H, Fukushima Y, Kobuchi S, Koyama S, Nishide M, Nakanishi Y, Izumi M, Naito M, Maruyama K, Okuno T, Kumanogoh A. Endothelial semaphorin 6D controls immune responses under cold stress through regulation of sympathetic innervation. Journal of Immunology 215, vkaf362 (2026).

84 Mori D, Sax N, Shimada N, Kuwabara M, Ebina I, Omiya R, Hattori K, Shinnakasu R, Yamashita K, Yamasaki S, Kurosaki T, Ise W. Epitope specificity shapes the CD4$^+$ T-cell response to influenza virus infection in mice. International Immunology, 38, iaf006 (2026).

85 Morigo A, Teppa RE, Nagae M, Yagi H, Kizuka Y, Harduin-Lepers A. Evolutionary analyses of the animal glycosyltransferase family 54 reveals two β1,4-N-acetylglucosaminyltransferase families. iScience 28, 113788 (2025).

86 Mudjahid M, Frediansyah A, Ophinni Y, Nainu F. Drosophila melanogaster as a prospective model organism for monkeypox virus research. Frontiers In Microbiology 16, 1696236 (2025).

87 Mudjahid M, Latada NP, Ophinni Y, Nainu F. Drosophila-based screening of herbal compounds targeting FOXO signaling pathway in type 2 diabetes mellitus. Frontiers In Pharmacology 16, 1621414 (2025).

88 Mukai M, Takahashi H, Kubo Y, Asahina Y, Iriki H, Nomura H, Kamata A, Ito H, Kurebayashi Y, Yamagami J, Mikami N, Sakaguchi S, Amagai M. Conversion of pathogenic T cells into functionally stabilized Treg cells for antigen-specific immunosuppression in pemphigus vulgaris. Science Translational Medicine 17, eadq9913 (2025).

89 Murakami T, Yamaguchi Y, Amiya S, Yoshimine Y, Nameki S, Okita Y, Kato Y, Hirata H, Takeda Y, Kumanogoh A, Morita T. CD147-high classical monocytes: a cellular biomarker for COVID-19 disease severity and treatment response. Inflammation and Regeneration 45, 8 (2025).

90 Murata A, Tokoyoda K. CD4$^+$ skin resident memory T cells preferentially colocalize with dermal Folr2hi macrophages in contact hypersensitivity. Frontiers In Immunology 16, 1590687 (2025).

91 Nagata S, Ishikawa-Yamauchi Y, Katagiri K, Sato T, Ikawa M, Ogawa T. Optimization of oxygen concentration and glycosphingolipid effects on spermatogenesis in mouse testicular culture†. Biology of Reproduction 114, 1079-1090 (2026).

92 Nakagawa H, Fujita Y, Yamashita T. Recovery of Motor Function via Intraspinal Detour Circuits following Unilateral Spinal Cord Injury. European Neurology 89, 22-32 (2026).

93 Nakahashi R, Matoba H, Sakai Y, Miura T, Moriyama T, Yoritate M, Yamasaki S, Hirai G. Linkage-Editing of 6,6'-Diacyl Neotrehalose and Evaluation of Mincle Activation Ability. Chemistry-An Asian Journal 21, e70412 (2026).

94 Nakanishi K, Ajiro T, Yukishima K, Tsukamoto Y, Kikuta J, Sawa S, Tomura M, Kinoshita N, Shimanuki W, Suzuki A, Arai S, Maeshima K, Ichisawa T, Katakai T, Hayasaka H, Ishii M, Umemoto E. Pyruvate-GPR31 axis induces LysoDC dendrite protrusion to M-cell pockets for effective immune responses. Gut Microbes 17, 2536089 (2025).

95 Nakano T, Bono K, Ueda J, Ohmi M, Saito S. Measurement of Glutamate Suppression in a 6-OHDA-Induced Dopamine Deficiency Rat Model Following Acute Single-Dose L-DOPA Using GluCEST/MRS. Biomedicines 13, 2761 (2025).

96 Namba S, Sonehara K, Koyanagi YN, et al. A cross-population compendium of gene-environment interactions. Nature 651, 688-697 (2026).

97 Natsume-Kitatani Y, Itoh MN, Takeda Y, et al. Subset binding enables detection of multimodal patient subgroup patterns and drug target discovery in idiopathic pulmonary fibrosis. Briefings In Bioinformatics 27, bbag153 (2026).

98 Natsume-Kitatani Y, Kobiyama K, Igarashi Y, Aoshi T, Nakatsu N, Tripathi LP, Ito J, Nyström-Persson J, Kosugi Y, Osorio RSA, Nagao C, Temizoz B, Kuroda E, Standley DM, Kiyono H, Nakanishi K, Uematsu S, Hamaguchi I, Yasutomi Y, Kunisawa J, Yamasaki S, Coban C, Yamada H, Mizuguchi K, Ishii KJ. An adjuvant database for preclinical evaluation of vaccines and immunotherapeutics. Cell Chemical Biology 32, 1075-1088 (2025).

99 Natsuyama T, Ueda J, Yabata I, Sawaya R, Itagaki K, Saito S. Multiparametric Evaluation of Drug-Induced Acute Kidney Injury Using Preclinical 7T Magnetic Resonance Imaging in Rat Models. Metabolites 15, 593 (2025).

100 Negishi H, Wada Y, Shirasaki Y, et al. cGAS-IFN-I responses by extracting nuclear DNA from dying cells via nucleocytosis. Nature Communications 17, 1658 (2026).

101 Niitsu T, Kataoka T, Fukushima K, Motooka D, Shichino S, Natsume-Kitatani Y, Kitamura H, Niwa T, Baba T, Okuzaki D, Kumanogoh A, Akira S, Okudela K, Ogura T. Spatial transcriptomics identifies SPARC as a prognostic marker in interstitial lung diseases. Journal of Pathology 267, 79-91 (2025).

102 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. Nature Communications 16, 3581 (2025).

103 Noguchi E, Morii W, Kitazawa H, Hirota T, Sonehara K, Masuko H, Okada Y, Hizawa N. A genome-wide meta-analysis reveals shared and population-specific variants for allergic sensitization. Journal of Allergy and Clinical Immunology 155, 1321-1332 (2025).

104 Nomura Y, Oda S, Matsumoto H, Togami Y, Shimazaki J, Okuzaki D, Ogura H, Oda J. Leukocyte mRNA sequencing reveals unfolded protein response activation in severe heat stroke in Japan. Frontiers In Cell and Developmental Biology 13, 1640477 (2025).

105 Oda S, Matsumoto H, Togami Y, Yoshimura J, Ito H, Onishi S, Muratsu A, Mitsuyama Y, Okuzaki D, Ogura H, Tanaka S, Oda J. mRNA-miRNA integration analysis of T-cell exhaustion in sepsis from community-acquired pneumonia. Acute Medicine & Surgery 12, e70054 (2025).

106 Ohtake Y, Norikami N, Hong B, Manabe K, Itokazu T, Yamashita T. Microglia-T cell interactions drive α-synuclein pathology in a Parkinson's disease mouse model. Journal of Neuroinflammation 23, 110 (2026).

107 Okamoto H, Li S, Nakamura Y. The Role of Skin Dysbiosis and Quorum Sensing in Atopic Dermatitis. JID Innovations 5, 100377 (2025).

108 Okamoto H, Nakamura Y. Dysbiosis in the Pathogenesis of Atopic Dermatitis. Journal of Dermatology 53, 388-398 (2026).

109 Okamura Y, Nakanishi K, Inada R, Maeda R, Maeshima K, Mizutani M, Ohashi W, Ikawa M, Sugiura Y, Takeda K, Umemoto E. GPR35 mediates monocyte recruitment to the sites of Listeria monocytogenes infection. Cellular and Molecular Life Sciences 82, 433 (2025).

110 Okumura T, Kumamoto Y, Smith NI, Fujita K. High-throughput spontaneous Raman imaging of biological specimens with water background reduction. Biomedical Optics Express 17, 160-171 (2026).

111 Onishi K, Itagaki K, Kusaka S, Nakano T, Ueda J, Saito S. Evaluation of the Effect of X-Ray Therapy on Glioma Rat Model Using Chemical Exchange Saturation Transfer and Diffusion-Weighted Imaging. Cancers 17, 2578 (2025).

112 Ono R, Tokuoka S, Tachibana M, Ishii KJ, Sakurai F, Mizuguchi H. Oncolytic adenovirus serotype 35 mediated tumor growth suppression via efficient activation of antitumor immunity. Journal for Immunotherapy of Cancer 13, e006558 (2025).

113 Ono Y, Wada S, Kobayashi Y, Ogi M, Fukushi Y, Tanimura K, Arase H, Yoshino O, Yamada H. Pregnancy outcomes in women with anti-β2-glycoprotein I/human leukocyte antigen-DR autoantibodies receiving assisted reproductive technology: a prospective cohort study. Frontiers In Immunology 16, 1626862 (2025).

114 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, 889-908 (2025).

115 Osuka RF, Nagae M, Nakano M, Tanigawa S, Ono K, Tsuji Y, Ito Y, Takahashi K, Nishinakamura R, Kizuka Y. Selective modification of glycoprotein substrates by GnT-V in mouse kidney. iScience 28, 113894 (2025).

116 Park S, Lee HY-. Emerging applications of the tropylium ion as reagent, catalyst, and chromophore. Bulletin of The Korean Chemical Society 47, 115-131 (2026).

117 Pennock ND, Qian YM, Ishihara K, Nakamura Y, Cross E, Sakaguchi S, White JT. Thymically imprinted heterogeneity results in differential Treg induction and stability of effector identity. Cell Reports 44, 115791 (2025).

118 Pizzuto M, Monteleone M, Burgener SS, Began J, Kurera M, Chia JR, Frampton E, Crawford J, Oliveira M, Kenney KM, Coombs JR, Yamamoto M, Man SM, Broz P, Pelegrin P, Schroder K. Cardiolipin inhibits the non-canonical inflammasome by preventing LPS binding to caspase-4/11. Embo Journal 44, 4419-4442 (2025).

119 Priest D, Wing J. Heterogeneity of memory B cells in human blood. International Immunology, 38, 348–356 (2026).

120 Rahmawati FN, Takakura N. Development and aging of resident endothelial stem cells in pre-existing blood vessels. Experimental Hematology 148, 104795 (2025).

121 Reja SI, Hori Y, Takeda Y, Nishiura M, Minoshima M, Kikuchi K. Controlling Intramolecular Rotation with Five-Membered Heterocycles Facilitates the Design of Highly Cell-Permeable Xanthene-Based Fluorogenic Probes. Journal of the American Chemical Society 147, 47997-48012 (2025).

122 Rowntree LC, Allen LF, Hagen RR, et al. HLA-B*15:01-positive severe COVID-19 patients lack $CD8^+$ T cell pools with highly expanded public clonotypes. Proceedings of the National Academy of Sciences of the USA 122, e2503145122 (2025).

123 Sakoguchi A, Chamberlain SG, Morch AM, Widdess M, Harrison TE, Dustin ML, Arase H, Higgins MK, Iwanaga S. RIFINs displayed on malaria-infected erythrocytes bind KIR2DL1 and KIR2DS1. Nature 643, 1363–1371 (2025).

124 Sato G, Yamamoto Y, Sonehara K, et al. Genetic regulation across germline and somatic variation on the Y chromosome contributes to type 2 diabetes. Nature Medicine 32, 894–905 (2026).

125 Sawasaki F, Sato A, Shimizu A, Matsumoto S, Kawamoto I, Murase M, Itagaki I, Tsuchiya H, Ishigaki H, Ueda N, Toyoda I, Itoh Y, Okuzaki D, Ema M, Ogita H. Suppression of the neutrophil-derived S100A8/A9 complex ameliorates doxorubicin-induced cardiomyopathy in non-human primates. Biochemical Pharmacology 243, 117484 (2026).

126 Schutt CR, Birol D, Lu XY, Yamasaki S. The presenting HLA determines fidelity of SARS-CoV-2 spike protein epitope prediction. Vaccine 61, 127381 (2025).

127 Shibahara T, Temizoz B, Egashira S, Hosomi K, Park J, Surucu N, Björk A, Sag E, Doi T, Ekinci RMK, Balci S, Versnel MA, Kunisawa J, Yamamoto M, Hayashi T, Ito S, Kamiyama Y, Kobiyama K, Katsikis PD, Coban C, Gursel M, Ozen S, Nishida S, Kumanogoh A, Ishii KJ. Microbial dysbiosis fuels STING-driven autoinflammation through cyclic dinucleotides. Journal of Autoimmunity 154, 103434 (2025).

128 Shimagami H, Nishimura K, Matsushita H, et al. Single-cell analysis reveals immune cell abnormalities underlying the clinical heterogeneity of patients with systemic sclerosis. Nature Communications 16, 4949 (2025).

129 Shinjyo N, Kimura H, Yoshihara T, Suzuki J, Yamaguchi M, Kawabata S, Okabe Y. Aldehyde metabolism governs resilience of mucociliary clearance to air pollution exposure. Journal of Clinical Investigation 135, e191276 (2025).

130 Shirai Y, Enomoto T, Takeda Y, Edahiro R, et al. Serum vesicle biomarkers reflect the disease activity of idiopathic pulmonary fibrosis. Journal of Translational Medicine 23, 1102 (2025).

131 Shoshihara N, Matsumoto K, Shiroyama T, Komuta K, Miyazaki A, Tamiya M, Tsukaguchi A, Tamiya A, Kuge T, Mihashi Y, Mori M, Yamauchi K, Suzuki H, Kinehara Y, Machiyama H, Tanaka S, Niki T, Kato S, Nishikawa Y, Osa A, Azuma K, Takeda Y, Kumanogoh A. Long-term survival comparison of first-line pembrolizumab versus pembrolizumab plus chemotherapy for patients with advanced non-small cell lung cancer: A multicenter propensity-matched cohort study. Lung Cancer 210, 108835 (2025).

132 Sonehara K, Watanabe R, Matsumura Y, et al. Whole-genome sequencing reveals rare and structural variants contributing to psoriasis and identifies CERCAM as a risk gene. Cell Genomics 5, 100978 (2025).

133 Sprenger C, Kanbara T, Yamada T, Morikawa Y, Koda K, Kashiwagi Y, Mano H, Morioka Y, Seymour B. Characterization of CNS Network Changes in Two Rodent Models of Chronic Pain. Biological & Pharmaceutical Bulletin 48, 1358-1374 (2025).

134 Suda N, Kumagai T, Kim Y, Park S, Iimura KI. Photoresponsive Helicity Control in Cholesteric Liquid Crystals Using a Chiral Arylazopyrazole Dopant: Chirality Amplification and Helix Inversion. ACS Applied Materials & Interfaces 17, 38797-38810 (2025).

135 Suzuki T, Miyata Y, Haga S, Itoh Y, Tanaka T, Hishinuma T, Orba Y, Eshita Y, Sakai Y, Kurosu T, Tajima S, Lim CK, Saijo M, Yamanaka A, Phanitchat T, Vargas REM, Okuzaki D, Sawa H, Satoh T, Akira S, Matsuura Y, Okamoto T. Selective TLR ligand stimulation enhances in vivo mosquito-borne flavivirus pathogenicity. Cell Reports 44, 116210 (2025).

136 Taguchi A, Misumi F, Teraguchi S, Nagamatsu T, Sakakibara S, Otani T, Ichinose M, Priest D, Nakajima K, Nakamura J, Sawada R, Suzutani T, Ikeda T, Nagura Y, Iriyama T, Okuzaki D, Okazaki H, Wing JB, Hirota Y, Osuga Y. Multifaceted profiling of virus-specific CD8 T cells reveals distinct immune signatures against cytomegalovirus infection states during pregnancy. iScience 28, 112416 (2025).

137 Taguchi T, Kawamura T, Mikami N, Torigata K, Harada A, Fujimura L, Ito E, Takeda M, Miki K, Sakaguchi S, Miyagawa S. Stable and functional regulatory T cell attenuates fibrotic remodeling in heart failure. Regenerative Therapy 31, 101079 (2026).

138 Takahashi Y, Wang QS, Hasegawa T, Namkoong H, Inoue F, Fukunaga K, Imoto S, Miyano S, Okada Y. JOB: Japan Omics Browser provides integrative visualization of multi-omics data. Bmc Genomics 26, 451 (2025).

139 Takamatsu N, Furumoto H, Ariga T, Iwaki M, Hayashi K. Stall force measurement of the kinesin-3 motor KIF1A using a programmable DNA origami nanospring. eLife 14, RP108477 (2026).

140 Takii T, Yamada H, Motozono C, Yamasaki S, Torrelles JB, Turner J, Kimishima A, Asami Y, Ohara N, Hida S, Hayashi H, Onozaki K. Mycobacterium tuberculosis bacillus induces pyroptosis in human lung fibroblasts. mSphere 10, e00110-25 (2025).

141 Tanida M, Takashima T, Tahara S, Kohara M, Kanai H, Suzuki M, Suzuki M, Hirokawa M, Suzuki A, Sato S, Okuzaki D, Nojima S, Matsui T, Inohara H, Morii E. Carbonic Anhydrase 12 as a Novel Prognostic Biomarker and Therapeutic Target for High-Risk Follicular Thyroid Carcinoma. Cancer Science 117, 257-271 (2026).

142 Tomimatsu M, Obana M, Tanaka S, Kajiura R, Nagano R, Matsumoto K, Yokota K, Kominami S, Ito T, Suzuki S, Motooka D, Liu YC, Seno S, Okuzaki D, Nagatomo I, Maeda M, Fukada SI, Okada Y, Fujio Y. Single-cell RNA sequencing analysis identified GARP-expressing myeloid cells that deteriorate postinfarct myocardial remodeling. American Journal of Physiology-Heart and Circulatory Physiology 330, H12-H30 (2026).

143 Tone M, Isono T, Yamamoto Y, Takeda Y, Shintani Y, Kumanogoh A, Wada H, Iwahori K. Lung tissue T cells are activated in chronic obstructive pulmonary disease with non-small cell lung cancer patients. Scientific Reports 15, 41209 (2025).

144 Tone M, Yano Y, Uchida J, Mori M, Wada H, Takeda Y, Kumanogoh A, Iwahori K. The relationship between galectin-1 expression and the efficacy of anti-PD-1 therapy for non-small cell lung cancer patients. Scientific Reports 15, 45305 (2025).

145 Tonomura S, Hattori Y, Ishibashi T, Ikeda S, Noda K, Chiba T, Kato Y, Asano R, Fukuma K, Edamoto-Taira Y, Motooka D, Inagaki T, Okazawa M, Nakamura S, Koga M, Toyoda K, Nomura R, Nakano K, Friedland RP, Takeda K, Takahashi R, Ihara M, Nakaoka Y. Oral Pathobiont Streptococcus Anginosus Is Enriched in the Gut of Stroke Patients and Predicts 2-Year Cardiovascular Outcome. Circulation Journal 89, 1931-1939 (2025).

146 Torigoe S, Salie S, Keeton R, Aylan B, Appelmelk B, Williams DL, Lowman DW, Sugiki T, Matsumoto S, Kawano A, Mizuno S, Matsuo K, Sondergaard JN, Wing JB, Höft MA, Shoesmith R, Ndengane M, Coussens AK, Willment JA, Gutierrez MG, Hoving JC, Yamasaki S, Brown GD. Mycobacterial α-glucans hijack dectin-1 to facilitate intracellular bacterial survival. Science Immunology 11, eadw0732 (2026).

147 Tort-Miró A, Alonso U, Martín-Mur B, Muñoz-Basagoiti J, Zeng Y, Marín-Moraleda D, Ezcurra E, Montaner-Tarbes S, Navas MJ, Muñoz M, Monleón P, González-Oliver J, Cano E, Vilalta C, Caballé M, Criado L, Kochanowski K, Accensi F, Aragón V, Correa-Fiz F, Esteve-Codina A, Rodríguez F, Argilaguet J. Inactivated Rothia nasimurium promotes a persistent antiviral immune status in porcine alveolar macrophages. Frontiers In Immunology 16, 1584092 (2025).

148 Tosa I, Ono M, Dang AT, Wang ZY, Kimura M, Kitagawa W, Ishibashi K, Do HT, Zhao K, Hara ES, Asada N, Nagasawa T, Oohashi T, Ohara N, Kuboki T. BMP-2 generates a functional bone marrow niche by inducing the differentiation of local mesenchymal cells into CAR cells. Blood Advances 9, 3598-3612 (2025).

149 Toyofuku T, Ishikawa T, Kumanogoh A. Deletion of the plexin-D1 ectodomain leads to anoikis by suppressing integrin inside-out signaling. Molecular Biology of The Cell 36, ar71 (2025).

150 Tsuda T, Fujii S, Obata S, Takeda K, Hayama M, Maeda Y, Nakatani A, Umeda N, Saito M, Fujii K, Kishikawa T, Tanaka H, Hosokawa K, Sato T, Takenaka Y, Okuzaki D, Nojima S, Ishii M, Inohara H. Central compartment of nasal cavity-derived MMP-9 enhances mixed-type 2 inflammation in eosinophilic chronic rhinosinusitis. International Immunology 37, 555–565 (2025).

151 Tsuji K, Yamanaka M, Kumamoto Y, Tamura S, Miyamura W, Kubo T, Mizushima K, Kono K, Hirano H, Shiozaki M, Zhao XW, Xi HQ, Sugiura K, Fukushima S, Kunimoto T, Tanabe Y, Nishida K, Mochizuki K, Harada Y, Smith NI, Heintzmann R, Yu ZH, Wang MC, Nagai T, Tanaka H, Fujita K. Time-deterministic cryo-optical microscopy. Light-Science & Applications 14, 275 (2025).

152 Tsuji N, Itagaki K, Yuto N, Xinli L, Bono K, Banura N, Ueda J, Saito S. Chemical exchange saturation transfer imaging and diffusion weighted imaging for colon 26 tumor bearing mice. Scientific Reports 16, 1107 (2025).

153 Tsujimoto K, Ebina K, Okamura S, Okita Y, Etani Y, Yamamoto W, Onishi A, Onizawa H, Shirasugi I, Nakano N, Kotani T, Hiramatsu Y, Hashimoto M, Okano T, Nozaki Y, Ashida C, Son Y, Tanaka A, Hara R, Okada S, Kumanogoh A. Sustained efficacy of second-line JAK inhibitors in patients with rheumatoid arthritis: insights from the ANSWER cohort. Rheumatology 64, 4207-4217 (2025).

154 Tsujioka H, Yamashita T. Mapping of projection of sprouting neuron in neonate and adult mice after pyramidotomy. Experimental Neurology 393, 115386 (2025).

155 Tung NTC, Nogami M, Iwasaki M, Yahara Y, Seki S, Makino H, Kamei K, He ZY, Kawaguchi Y. M2-like macrophages derived from THP-1 cells promote myofibroblast differentiation of synovial fibroblasts in association with the TGF-β1/SMAD2/3 signaling pathway. Scientific Reports 15, 25505 (2025).

156 Uno H, Itokazu T, Yamashita T. Formyl peptide receptor 2 antagonist WRW4 ameliorates diabetes-induced cognitive decline in mice. Neuroscience Research 218, 104932 (2025).

157 Wakita M, Ito K, Fujii K, Sakamoto D, Mikawa T, Sugawara S, Zhou XY, Park JH, Miyagawa H, Motooka D, Ogasawara E, Ishihara N, Takahashi A, Kondoh H, Hara E. Comparative analysis of senolytic drugs reveals mitochondrial determinants of efficacy and resistance. Nature Aging 6, 316–328 (2026).

158 Wang HF, Zhou H, Yao XS. Different Species of Bats: Genomics, Transcriptome, and Immune Repertoire. Current Issues In Molecular Biology 47, 252 (2025).

159 Wang M, Rahmawati FN, Li WT, Bal Z, Sitompul FN, Muramatsu F, Jia WZ, Takakura N. APJ regulates the balance between self-renewal and differentiation of vascular endothelial stem cells. Inflammation and Regeneration 45, 25 (2025).

160 Wannigama DL, et al. Intranasal phage therapy overcomes antibody neutralization challenges in pulmonary Pseudomonas aeruginosa infections. Archives of Microbiology 207, 310 (2025).

161 Watanabe T, Nagai M, Ishibashi Y, Iwasaki M, Mizoguchi M, Nagata M, Imai T, Takato K, Imamura A, Kakuta Y, Teramoto T, Tani M, Matsuda J, Ishida H, Yamasaki S, Okino N, Ito M. Vacuolar sterol β-glucosidase EGCrP2/Sgl1 deficiency in Cryptococcus neoformans: Dysfunctional autophagy and Mincle-dependent immune activation as targets of novel antifungal strategies. PLOS Pathogens 21, e1013089 (2025).

162 Wee WA, Andini TM, Kumagai T, Chinnathambi S, Pandian GN, Millius A, Sugiyama H, Standley DM, Park S. Tiny but mighty! N,N-dimethyl-4-(5-nitrothiophen-2-yl)aniline, a push-pull fluorescent dye for lipid droplet imaging. Analytica Chimica Acta 1359, 344130 (2025).

163 Wei J, Moon J, Yasumizu Y, Zhang L, Radassi K, Buitrago-Pocasangre N, Deerhake ME, Strauli N, Chen CW, Herman A, Pedotti R, Raposo C, Yim I, Pappalardo J, Longbrake EE, Sumida TS, Axisa PP, Hafler DA. Transcriptomic profiling after B cell depletion reveals central and peripheral immune cell changes in multiple sclerosis. Journal of Clinical Investigation 135, e182790 (2025).

164 Wu Y, Minoshima M, Kikuchi K. Lipid Bilayer-Coated Core-Shell Silica Nanoparticles with Enhanced Clearance and Biocompatibility for High Sensitivity 19F Magnetic Resonance Imaging. Analysis & Sensing 6, e202500178 (2026).

165 Xue Y, Tai YK, Yamamoto H, Mori D, Sakai K, Miyazaki T, Owa M, Kometani K, Ebina I, Omiya R, Hattori K, Inoue T, Ise W, Shinnakasu R, Kurosaki T. T-cell help is a limiting factor for rare anti-influenza memory B cells to re-enter germinal centers and generate potent broadly neutralizing antibodies. International Immunology 38, 383–395 (2026).

166 Yabata I, Ueda J, Takao T, Nakasone S, Tarewaki H, Koyama Y, Saito S. Reproducibility of native T1 value measurements across cardiac phases and slice positions using a 1.5T magnetic resonance system. Radiological Physics and Technology 19, 342-349 (2026).

167 Yamaguchi Y, Amiya S, Inokuchi S, Nagao S, Kosaka K, Nameki S, Murakami T, Yoshimine Y, Okita Y, Kawasaki T, Morita T, Tsujimoto K, Fujimoto J, Nishide M, Nishida S, Narazaki M, Kato Y, Kumanogoh A. Distinct trajectories of humoral immune responses after SARS-CoV-2 mRNA vaccination in autoimmune inflammatory rheumatic diseases: A group-based trajectory analysis. Vaccine 66, 127771 (2025).

168 Yamamoto Y, Shirai Y, Sonehara K, Namba S, Ojima T, Yamamoto K, Edahiro R, Suzuki K, Kanai A, Matsuda K, Morisaki T, Okada Y, Oda Y, Suzuki Y, Morisaki T, Narita A, Takeda Y, Tamiya G, Yamamoto M, Matsuda K, Kumanogoh A, Yamauchi T, Kadowaki T, Okada Y. Dissecting cross-population polygenic heterogeneity across respiratory and cardiometabolic diseases. Nature Communications 16, 3765 (2025).

169 Yamashita E, Hashimoto S, Abe H, Sudo T, Okuzaki D, Okawa T, Ishii M. Red Blood Cell-Mediated Enhancement of Hematopoietic Stem Cell Functions via a Hes1-Dependent Pathway. Faseb Journal 39, e71022 (2025).

170 Yanagiya R, Kato H, Ninomiya A, Ueno M, Kanamori A, Miyatake Y, Oka M, Ishii K, Matsuura T, Nakagawa S, Hirao A, Onizuka M, Kotani A. Revised model for cell cycle regulation by iron: differential roles between transferrin and ferritin. Redox Biology 85, 103727 (2025).

171 Yano K, Takashima T, Feng ZZ, Kohara M, Nagata H, Okuzaki D, Shintani Y, Morii E. Investigating the Role of Long Non-Coding RNA HAGLR and Its Target NT5E in Alveolar Epithelial Injury. Pathology International 75, 613-623 (2025).

172 Yap SL, Dyett B, Hobro AJ, Nguyen H, Smith NI, Drummond CJ, Conn CE, Tran N. The Internal Nanostructure of Lipid Nanoparticles Influences Their Diverse Cellular Uptake Pathways. Small 21, 2500903 (2025).

173 Yasuda S, Banura N, Ito M, Bono K, Sawaya R, Ueda J, Saito S. In-vivo assessment of vascular endothelial injury in a rat model of unilateral carotid artery injury using 4D-flow MRI. Scientific Reports 15, 18571 (2025).

174 Yasuda S, Ito M, Banura N, Ueda J, Hashido T, Kamada Y, Saito S. Differences in blood flow velocity measurements between 4D-flow MRI and doppler US in rat carotid arteries. Radiological Physics and Technology, 19, 499–508 (2026).

175 Yin WQ, Okamoto K, Terashima A, Pluemsakunthai W, Ono T, Ito-Kureha T, Akira S, Hashizume Y, Baron R, Ueha S, Matsushima K, Matzuk MM, Mishina Y, Takayanagi H. Activin A secretion by muscle-repairing macrophages induces heterotopic ossification in mice. Journal of Clinical Investigation 136, e193797 (2026).

176 Yokoyama Y, Inoue A, Yamamoto H, Kouda S, Irie Y, Yang RJ, Zhang YJ, Tsujimoto M, Nagata N, Morimoto Y, Hata T, Okuzaki D, Shibata S, Yamamoto H, Mori M. The miR-29b Byproduct MIRTX Shows Superior Anti-tumor Activity, Compared to miR-29b-3p, in Pancreatic Cancer Cells. Anticancer Research 46, 619-632 (2026).

177 Yoshikawa FSY, Yabe R, Torigoe S, Yamasaki S, Saijo S. The C-type lectin receptor Dcir (Clec4a2) restrains Aspergillus fumigatus elimination by limiting the degranulatory activity of neutrophils. Frontiers In Immunology 16, 1639400 (2025).

178 Yoshioka Y, Nishinaka-Yoshioka A, Kobiyama K, Hayashi T, Kidani Y, Yanagida Y, Kasahara J, Tsujii K, Asaoka Y, Kuroda N, Kugimiya A, Osawa H, Yoshimura A, Onishi M, Nakagawa T, Ishida S, Omoto S, Nagira M, Coban C, Ishii KJ. IL-1 delineates squalene-based adjuvant efficacy and reactogenicity in a cell-type-specific manner. npj Vaccines 11, 67 (2026).

179 Zaike T, Kotaki S, Araragi M, Ariji Y, Saito S. Investigation of imaging conditions for dental MRI using 3T-MRI system with microscopy coil in clinical situation. Radiological Physics and Technology 18, 570-581 (2025).

180 Zhang JJ, Qin SS, Huang XH, Hilmayanti E, Hu F, Luan XH, Ye TZ, Li FZ, Yang YY, Liu N, Kabayama K, Fukase K, Yu F. Preclinical evaluation of [211At]At-AuNP-ABDMPL16 for targeted alpha therapy in Melanoma. European Journal of Nuclear Medicine and Molecular Imaging 52, 4497-4510 (2025).

181 Zhou H, Jiko C, Gerle C, Lefranc MP, Katoh K, Standley DM. From benchmarking alignment of genome assemblies to IMGT annotation: the paradigm of the bovine Bos taurus T cell receptor (TRG) locus. Bmc Genomics 26, 809 (2025).

The articles were published between April, 2025 and March, 2026. The data was acquired using Web of ScienceTM Core Collection on April 30, 2026, and sorted by alphabetical order of the first authors.

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Edit : Research Planning & Management Office, IFReC
Published in June, 2026