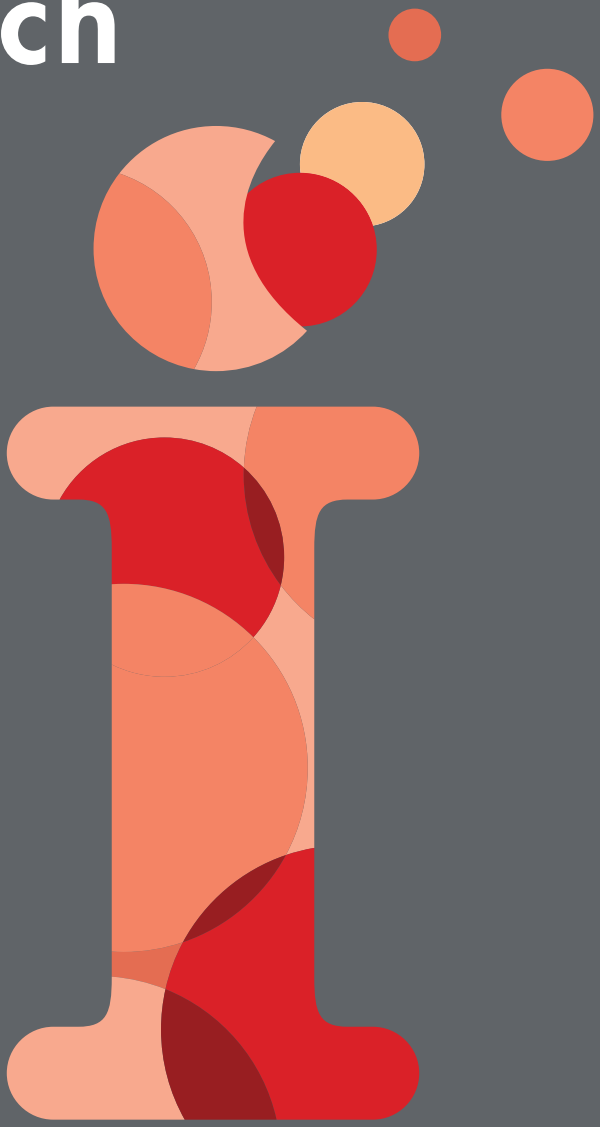
World Premier International
Research Center

Osaka University

Immunology Frontier Research Center



Annual Report of IFReC 2018–2019

Digest edition

wpi
World Premier International
Research Center Initiative

WPI Osaka University
iFReC

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Message from the Director

As the Director of the Immunology Frontier Research Center (IFReC) at Osaka University, I am very pleased to present the IFReC annual report for fiscal 2018.

From 2017, IFReC has been one of the members of the "WPI Academy". Furthermore, IFReC created a new mark in its history with a novel academic-industry partnership agreement. This governance system is without precedent and has attracted the attention of universities and enterprises as a way to show the new direction of research universities.

IFReC hopes to expand as a center that can provide a wide field for collaborative research. As part of this strategy, IFReC newly formed academic collaborative partnerships with the University of Bonn and Heidelberg University, Germany in 2018. We also hope IFReC will be a place along the career paths that focuses the capabilities of a wide variety of talented international researchers.

From July 2019, Professor Kiyoshi Takeda will succeed me as the director of IFReC. In the next decade, IFReC will aspire to further development under the leadership of Prof. Takeda, who is a world top class immunologist in the fields of innate immunity and gut immunity.

We are committed to continuing contributions to scientific advances through research and education and evolvement into a world top immunology research center.

Shizuo Akira, MD, PhD
Director
WPI Immunology Frontier Research Center

Committee and Advisory Board for IFReC

World Premier International Research Center Initiative (WPI)

Program Director

As of Mar. 2019

Akira Ukawa	Director, Center for World Premier International Research Center Initiative, JSPS, Japan

Deputy Program Director

Minoru Yoshida	Group Director, Chemical Genomics Research Group, RIKEN, Center for Sustainable Resource Science, Japan

Program Committee Members

Rita Colwell	Distinguished Professor, University of Maryland, USA
Richard Dasher	Consulting Professor, Stanford University, USA
Victor Joseph Dzau	President, National Academy of Medicine, USA
Michinari Hamaguchi	President, Japan Science and Technology Agency (JST), Japan
Toshiaki Ikoma	Professor Emeritus,The University of Tokyo, Japan
Maki Kawai	Director General, Institute for Molecular Science, National Institutes of Natural Sciences, Japan
Klaus von Klitzing	Director, Max Planck Institute for Solid State Research, Germany Nobel Laureate in Physics (1985)
Makoto Kobayashi	Honorary Professor Emeritus, High Energy Accelerator Research Organization, Japan Nobel Laureate in Physics (2008)
Kiyoshi Kurokawa	Professor Emeritus, National Graduate Institute for Policy Studies, Japan
Chuan Poh Lim	Chairman, Agency for Science, Technology and Research, Singapore
Hiroshi Matsumoto	President, RIKEN, Japan
Ryozo Nagai	President, Jichi Medical University, Japan
Michiharu Nakamura	Counselor to the President, JST, Japan
〈**Chairperson**〉 **Ryoji Noyori**	Director-General, Center for Research and Development Strategy, JST, Japan Nobel Laureate in Chemistry (2001)
Norihiko Suzuki	Chair of the Board/President, Akita International University
Harriet Wallberg	Former President, Karolinska Institutet, Sweden
Jean Zinn-Justin	Scientific Adviser, IRFU/CEA, France

WPI Academy

In FY 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.

The five WPI centers including IFReC are regarded to have achieved "world-premier status", and thus became the initial members of the WPI Academy.

In the decade ahead, the research institutes of WPI and WPI Academy will work together to hold public relations and outreach activities.

Academy Director

As of Mar. 2019

Toshio Kuroki	Special Advisor, Research Center for Science Systems, JSPS, Japan

Academy Officer for IFReC

Takehiko Sasazuki	University Professor, Institute for Advanced Study, Kyushu University, Japan

International Scientific Advisory Board from abroad

As of Mar. 2019

Jeffrey Ravetch	The Rockefeller University, USA	**Immunology**
Christopher Goodnow	The Australian National University, Australia	**Immunology**
Richard Locksley	University of California, San Francisco, USA	**Immunology**
Lewis L. Lanier	University of California, San Francisco, USA	**Immunology**
Anne O'Garra	The Francis Crick Institute, UK	**Immunology**
Yale Goldman	University of Pennsylvania, USA	**Imaging**

Interview with an IFReC researcher

Dr. Ee Lyn Lim (Advanced Postdoc* Fellow of IFReC)

When did you decide to get into research?

I had a wonderful professor during my undergraduate studies at the University of Oxford, who worked very hard for all his students to gain experience in world-class research labs. Under his guidance I developed the understanding and confidence to start my research career.

How did you first learn about IFReC?

During my PhD I learned of the joint Winter School program organized between IFReC and Singapore Immunology Network (SIgN), which I thought was a great international collaboration. When I became interested in regulatory T cell (Treg) research, I realized that Professor Sakaguchi is based at IFReC, which made me determined to come here.

What kind of research were you doing before you arrived at IFReC?

During my PhD, I studied a mouse model of PI-3-kinase δ (PI3Kδ) inactivation, which confers resistance to many types of syngeneic mouse tumors. We hypothesized that we would be able to obtain the best results in treating cancer by combining PI3Kδ inhibition with enhancement of $CD8^+$ T cells using vaccines or checkpoint blockade, but surprisingly we found that PI3Kδ-deficient $CD8^+$ T cells were unable to respond to therapeutic enhancement.

**Advanced Postdoc position of IFReC*
This position provides early-career researchers with an almost-unparalleled degree of freedom. With access to top-notch facilities, generous financial support, and some of the most renowned immunologists in the world, we are in the envied position of being able to chase whatever scientific question piques our curiosity.

Dr. Lim at IFReC Research Building

What kind of research are you currently doing?

My current work investigates a different aspect of the topic I studied in my PhD. Rather than targeting the $CD8^+$ T cells, I believe the key to how PI3Kδ inactivation protects mice against tumor growth lies in a reduced function of Tregs. However, we still do not understand how PI3Kδ-deficient Tregs are different from normal Tregs, as they appear to be normal under many methods of measurement. This is the question I would like to answer during my time at IFReC.

Did you have any reservations about doing research in Japan?

Japanese people are famous globally for working extremely long hours. I had also heard that discrimination against women in the workplace is relatively common in Japan. I am happy to say that we are free to set our own working hours in the Sakaguchi lab, and I have not had any bad experiences personally as a female member of the lab. I am also glad that IFReC and Osaka University have policies which encourage both a healthy working life and gender equality.

What makes you glad you came to Japan?

I have always been interested in Japanese culture, but often it is portrayed in a very one-dimensional manner to people outside Japan. I am happy for the opportunity to gain a deeper and more nuanced understanding of the rich, complex culture and society of Japan.

What do you enjoy in daily life or when doing research in Japan?

I very much enjoy traveling around Japan. I have visited 30 prefectures in Japan so far, and am hoping to visit all of them in the future! I think it is a unique privilege to be able to hop on a Shinkansen on any weekend, and enjoy a variety of gorgeous scenery and special local food.

Do you have any difficulties in daily life or when doing research in Japan?

It is a bit difficult to get used to the social aspect of Japan, as Japanese people are socially very reserved, which means it is rare to have casual conversations. Every time I come back to Japan from overseas, I am surprised at how quiet my office is!

What kind of researcher would you like to become in the future?

It is difficult to predict what will happen in my career in the future! I hope I am able keep contributing to scientific knowledge and human health. Most importantly, I hope I become a kind mentor to future students and young researchers.

Short trip to Nara, renowned for its free-roaming deer and world heritages

IFReCgram

Host Defense

Shizuo Akira
Host Defense

#InnateImmunity
#PathogenRecognition
#macrophage

Immunoglycobiology

Taroh Kinoshita
Immunoglycobiology

#GPI-anchor
#ParoxysmalNocturnalHemoglobinuria

Immunopathology

Atsushi Kumanogoh
Immunopathology

#ImmuneSemaphorin
#AutoimmuneDiseases
#T-cellActivation

Immunochemistry

Hisashi Arase
Immunochemistry

#MHC #neo-self
#MisfoldedProtein
#malaria

Immune Regulation

Tadamitsu Kishimoto
Immune Regulation

#rheumatism #IL-6
#Th17Differentiation

Mucosal Immunology

Kiyoshi Takeda
Mucosal Immunology

#gut immunity
#InflammatoryBowelDisease(IBD)
#microbiota

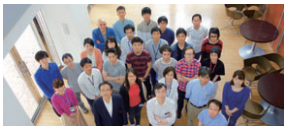
Immune Regulation

Hitoshi Kikutani
Immune Regulation

#SLE
#Anti-nuclearAntibody(ANA)

Experimental Immunology

Shimon Sakaguchi
Experimental Immunology



#Treg #ImmuneTolerance
#CancerImmunology

Cell Signaling

Takashi Saito
Cell Signaling

#T-cellActivation
#TCRSignal

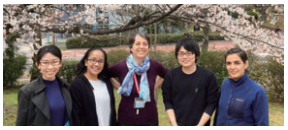
Lymphocyte Differentiation

Tomohiro Kurosaki
Lymphocyte Differentiation

#MemoryB-cell
#AntibodyProduction

Malaria Immunology

Cevayir Coban
Malaria Immunology



#MalariaParasite
#vaccine

Vaccine Science

Ken J. Ishii
Vaccine Science

#vaccine
#adjuvant

Immunoparasitology

Masahiro Yamamoto
Immunoparasitology

#parasite #toxoplasma
#ImmuneEvasion

Biochemistry & Immunology

Shigekazu Nagata
Biochemistry & Immunology

#macrophage
#CellDeathSignal
#apoptosis

Molecular Neuroscience

Toshihide Yamashita
Molecular Neuroscience

#CentralNervousSystem
#encephalomyelitis

Molecular Immunology

Sho Yamasaki
Molecular Immunology

#lectin
#NovelImmuneReceptor

Stem Cell Biology and Developmental Immunology

Takashi Nagasawa
Stem Cell Biology and Developmental Immunology

#CARCell #StemCell
#niche

Aging Biology

Eiji Hara
Aging Biology

#aging #SASP
#cancer

Oncogene Research

Masato Okada
Oncogene Research

#mTOR #SRC
#cancer

Signal Transduction

Nobuyuki Takakura
Signal Transduction

#BloodVessels #StemCell
#cancer

Cutaneous Immunology

Manabu Fujimoto
Cutaneous Immunology

#IntractableSkinDiseases
#allergy

Innate Immune Systems

Kazuyo Moro
Innate Immune Systems

#ILC2
#AutoimmuneDiseases

Human Immunology

James Wing

Daisuke Okuzaki
Human Immunology

#HumanDiseases
#SingleCell #genomics

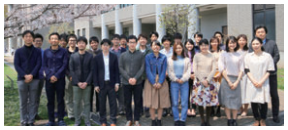
Single Molecule Imaging

Toshio Yanagida/
Ben Seymour
Single Molecule Imaging

#SingleMoleculeImaging
#MembraneProtein

Immunology and Cell Biology

Masaru Ishii
Immunology and Cell Biology



#osteoclast #LiveImaging
#CancerMetastasis

Nuclear Medicine

Jun Hatazawa
Nuclear Medicine

#PET/MRI #FBPA
#CancerTherapy

Chemical Imaging Techniquese

Kazuya Kikuchi
Chemical Imaging Techniques

#ChemicalBiology
#FluorescentProbe

Immune Response Dynamics

Kazuhiro Suzuki
Immune Response Dynamics

#AdrenergicRceptor
#LymphocyteTrafficking

Biophotonics

Nicholas Isaac Smith
Biophotonics

#LabelFree #RamanScattering
#IntraCellImaging

Systems Immunology

Daron M. Standley
Systems Immunology

#ImmuneRepertoire
#ReceptorModeling

Statistical Immunology

Yukinori Okada
Statistical Immunology

#StatisticalGenetics #BigData
#DiseaseRiskGenes

The 10th International Symposium of IFReC, co-hosted with Cluster Science Days 2018

The 10th International Symposium of IFReC was held on November 5th-6th, 2018 in the Biomedical Center (BMZ) at Venusberg Campus of the University Hospital Bonn. This was concurrently held as Cluster Science Day 2018 through joint organization with ImmunoSensation, University of Bonn. Thirty-five oral and 88 poster presentations including those of seven IFReC PIs were made for an audience of over 300 participants from University of Bonn and vicinal research institutes. IFReC, Research Institute for Microbial Diseases (RIMD) and Graduate School of Frontier Biosciences (FBS) of Osaka University jointly concluded an Academic Exchange Agreement with ImmunoSenation, which is one of the leading institutions in Immunology in Europe. The success of the symposium is expected to promote exchanges of young researchers and international collaboration.

- **Date :** **November 5-6, 2018**
- **Venue :** **Biomedical Center (BMZ) at of the University Hospital Bonn, Bonn, Germany**

Osaka-Heidelberg/Mannheim Symposium on Immune Plasticity

The Osaka-Heidelberg/Mannheim Symposium on Immune Plasticity was held on November 8th, 2018 at International Academic Forum Heidelberg (IWH) of Heidelberg University. A small group of approximately 50 participants permitted intense discussions with immunologists of Heidelberg University on the latest issues in immunology.

- **Date :** **November 8, 2018**
- **Venue :** **International Academic Forum Heidelberg, Heidelberg, Germany**

Next Gen Immunology in Health and Disease

Next Gen Immunology in Health and Disease was held on February 7th and 8th at Osaka International Convention Center, Osaka, Japan. Ten core researchers of top research institutes in Europe, two distinguished researchers in Japanese institutes and seven IFReC researchers were invited as speakers. The symposium had 195 participants including 55 international and 41 from industry or hospitals. The symposium could successfully promote interactions among researchers of IFReC and Europe for future international collaborations and of academia and industry/clinical domains for future collaborations for applied and translational research.

- **Date :** February 7-8, 2019
- **Venue :** Osaka International Convention Center (Grand Cube Osaka), Osaka, Japan

Day 1

Speaker	Title
Tadamitsu Kishimoto IFReC, Osaka University	**Keynote :** A possible therapeutic target, Arid5a for the treatment of inflammatory diseases associated with aberrant cytokine expression
Takashi Nagasawa IFReC/Graduate School of FBS/Medicine, Osaka University	Bone marrow microenvironmental niches for hematopoietic stem cells and immune cells
Kazuyo Moro RIKEN IMS, Japan	IL-4 Production of Group 2 Innate Lymphoid Cells
Chair : Wataru Ise (IFReC, Osaka University)	
Shimon Sakaguchi IFReC, Osaka University	Regulatory T cells in common autoimmune diseases
David Klatzmann Sorbonne University, France	On Treg-based therapies of autoimmune diseases
Federica Sallusto Universita della Svizzera Italiana/ ETH Zurich, Switzerland	Human Memory T Cell Subsets: from Phenotype to Function
Sjoerd Henricus van der Burg Leiden University, the Netherlands	Combination treatments to modulate the microenvironment and boost tumor-specific T cells
Chair: Kazuhiro Suzuki (IFReC, Osaka University)	
Tomohiro Kurosaki IFReC, Osaka University/RIKEN IMS, Japan	Selection mechanisms of germinal center cells into the memory B cell compartment
Hisashi Arase IFReC/RIMD, Osaka University	Paired receptors in host-pathogen interaction
Kiyoshi Takeda IFReC/Graduate School of Medicine, Osaka University	Regulation of immune responses by intestinal microbiota
Kenya Honda Keio University/RIKEN IMS, Japan	Gut microbiota-mediated immune modulation

Day 2

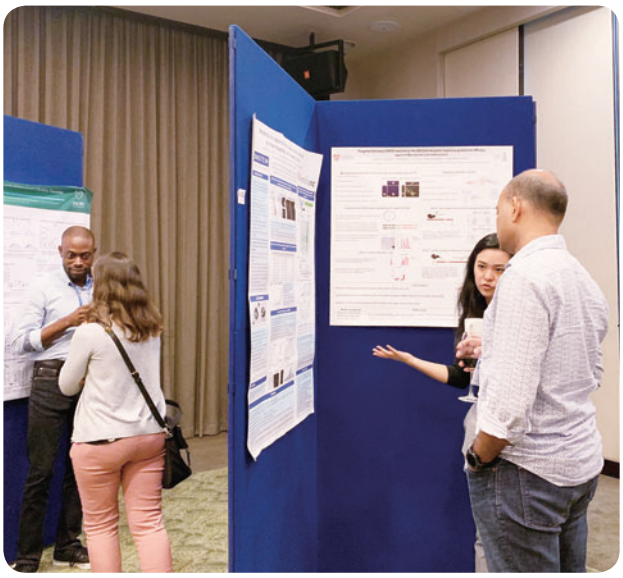
Speaker	Title
Chair : James Badger Wing (IFReC, Osaka University)	
Klaus Rajewsky Max Delbruck Center for Molecular Medicine, Germany	**Keynote :** Gene targeting: 30 years later
Gioacchino Natoli Humanitas University, Italy	Access to the genomic regulatory information and the control of inflammatory gene expression
Thomas Weichhart Medical University of Vienna, Austria	3M: Macrophages, mTOR and metabolism
Shizuo Akira IFReC, Osaka University	Towards understanding the mechanism of lung fibrosis
Chair : Takashi Satoh (IFReC, Osaka University)	
Ido Amit Weizmann Institute of Science, Israel	Single-cell genomics: A stepping stone for future immunology discoveries
Anna Katharina (Katja) A Simon The Kennedy Institute, University of Oxford, UK	Autophagy in the immune system
Eicke Latz University Hospital Bonn/German Center for Neurodegenerative Diseases /University of Massachusetts, USA	Regulation of inflammasome responses
Chair : Masahiro Yamamoto (IFReC, Osaka University)	
Petr Broz University of Lausanne, Switzerland	Regulation of Gasdermin-D-induced pyroptotic cell death
Sho Yamasaki IFReC/RIMD, Osaka University	Recognition of tissue damage via C-type lectin receptors

The 8th NIF Winter School on Advanced Immunology

The 8th NIF Winter School on Advanced Immunology was held from January 20 to 23, 2019 in Singapore. The NIF Winter School series is organized and held each year alternatively in Singapore and Japan in a collaboration with Singapore Immunology Network (SIgN). The scientific program comprised of 16 guest lectures, participants' short presentations and poster sessions. A group of 47 excellent students including four from IFReC were selected. The enthusiasm of the participants and the high scientific quality of the lectures and the presentations made the NIF Winter School an extremely successful event. The Winter School experience made a strong impact on all participants, by widening and deepening their understanding of immunology, furthering their commitment to excellence in scientific research, and creating many new friendships.

- **Date :** January 20-23, 2019
- **Venue :** Grand Copthorne Waterfront Hotel, Singapore

Lecturer	Title
Shizuo Akira (IFReC, Osaka University, Japan)	Understanding the molecular mechanism of lung fibrosis
Veronique Angeli (National University of Singapore, Singapore)	Hyaluronan receptor LYVE-1-expressing macrophage keeps our artery healthy
Hisashi Arase (IFReC, Osaka University, Japan)	LILR family receptor in host-pathogen interaction
Marc Bajenoff (Centre d'Immunologie de Marseille-Luminy, France)	Lymphatic endothelial cells constitute the niche for self-maintaining subcapsular sinus macrophages
Burkhard Becher (University of Zurich, Switzerland)	The T cell/Phagocyte Interface in Chronic Inflammation
Kenji Kabashima (SIgN, Singapore)	Cutaneous immune responses to external stimuli
Klaus Karjalainen (Nanyang Technological University, Singapore)	Maintenance of tissue-resident macrophages
Claudia Kemper (National heart, Lung and Blood Institute (NIH), USA)	The Force from within: unexpected roles for the complosome in normal cell physiology
Tomohiro Kurosaki (IFReC, Osaka University, Japan)	Fate decision of germinal center B cells
Claudia Mauri (University College London, UK)	Cellular and molecular characterization of regulatory B cells
Lai Guan NG (SIgN, Singapore)	Neutrophils: The Power of Many
Jeff Rathmell (Vanderbilt Institute of Infection, Immunology, and inflammation, USA)	Fueling T cells in Inflammation and Cancer
Amit Singhal (SIgN, Singapore)	Harnessing Host Immuno-metabolic circuits For Restricting Mycobacterium tuberculosis
Ashley ST John (Duke-NUS Medical School, Singapore)	Mast cell responses to virus infection
Sho Yamasaki (IFReC, Osaka University, Japan)	Recognition of intracellular metabolites through C-type lectin receptors
Simon Yona (University College London, UK)	Monocytes kinetics in health and disease



Visitors to IFReC

Two directors from Curie Institute

IFReC welcomed Dr. Eliane Piaggio and Dr. Ana-Maria Lennon-Duménil from the Curie Institute, France, in October 2018. IFReC and the Curie Institute confirmed the cooperative relationship in near future. We invited them as speakers for the IFReC seminar on October 29, 2018.

Courtesy call by Brunei Darussalam

Osaka University welcomed distinguished guests from three universities of Brunei Darussalam in August 2018. The office of Osaka University organized a signing ceremony for an inter-university exchange agreement and the joint symposium. Before the ceremony, IFReC received a courtesy call by the guests from Brunei Darussalam.

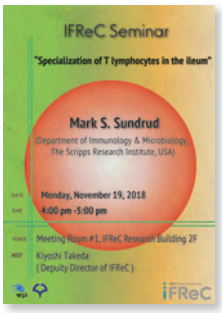
The 23rd Chinese University Student Delegation to Japan Project

Thirty-eight members of the 23rd Chinese University Student Delegation to Japan Project visited IFReC on November 28. The students attended a lecture by Dr. Naganari Ohkura and visited the Experimental Immunology laboratory, MRI imaging facility and the RIMD museum.

IFReC Seminars

IFReC holds seminars throughout the year with speakers from a variety of disciplines including immunology, imaging and informatics with the aim of promoting collaborative research, as well as to inspire and educate the next generation of scientists.

Since its establishment, IFReC has held more than a hundred seminars, which have served as a forum for effective interaction between researchers beyond national borders and academic disciplines. This program has certainly contributed to IFReC's mission of promoting internationalization and interdisciplinary research.



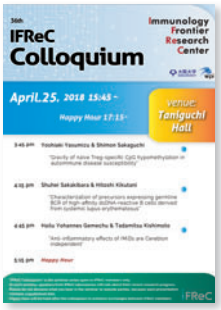
Date	Speaker	Title
May 21, 2018	Mahesh Desai (PI, Allergology - Immunology - Inflammation Research Unit, Luxembourg Institute of Health)	Diet-driven interactions of the gut microbiome with the intestinal mucus barrier
October 29, 2018	Eliane Piaggio (Director, Translational Immunotherapy Team, Curie Institute, France)	Targeting Tregs in cancer: a translational approach
October 29, 2018	Ana-Maria Lennon-Dumenil (Director, the Spatio-Temporal Regulation of Antigen Presentation and Cell Migration Team, Curie Institute, France)	Migration of dendritic cells under pressure
November 19, 2018	Mark S. Sundrud (Associate Professor, Department of Immunology & Microbiology, The Scripps Research Institute, USA)	Specialization of T lymphocytes in the ileum
February 22, 2019	Motohiko Kadoki (Massachusetts General Hospital / Broad Institute / Harvard Medical School, USA)	Inter-Organ Dialogues during Vaccination -Lessons from Organismal Systems Immunology-






IFReC Colloquia

IFReC colloquia are a series of discussion meetings for IFReC members held once every other month since FY2011. At each colloquium, three speakers from IFReC laboratories give talks about their latest research progress followed by intensive discussion. After the colloquium, a small social gathering is held to further the discussions and encourage the exchange among IFReC members in an informal setting. These events serve as a platform to promote fusion researches and deepen understanding of researches conducted in IFReC.



	Date	Speaker	Title
36th	April 25, 2018	Yoshiaki Yasumizu, Naganari Ohkura, and Shimon Sakaguchi (Experimental Immunology)	Gravity of naïve Treg-specific CpG hypomethylation in autoimmune disease susceptibility
		Shuhei Sakakibara and Hitoshi Kikutani (Immune Regulation)	Characterization of precursors expressing germline BCR of high-affinity dsDNA-reactive B cells derived from systemic lupus erythematosus
		Hailu Yohannes Gemechu and Tadamitsu Kishimoto (Immune Regulation)	Anti-inflammatory effects of IMiDs are Cereblon independent
37th	June 13, 2018	Takato Kusakabe and Ken Ishii (Vaccine Science)	R&D of Hydroxypropyl-β-Cyclodextrin (HP-β-CD) as a vaccine adjuvant <Hydroxypropyl-β-cyclodexrin (HP-β-CD) is an IL-33 inducer in the lung>
		Rouaa Beshr and Jun Hatazawa (Nuclear Medicine)	18F-FBPA PET/CT: to distinguish radiation-induced cerebral necrosis from recurrent brain tumor
		Katsumori Segawa and Shigekazu Nagata (Biochemistry & Immunology)	Phospholipid flippases enable precursor B cells to flee entosis
38th	August 29, 2018	Yukinori Okada (Statistical Immunology)	Genetic and phenotypic landscape of MHC in the Japanese population
		Masanari Seike and Takashi Nagasawa (Stem Cell Biology and Developmental Immunology)	Hematopoietic stem cell niche-specific Ebf3 maintains the bone marrow cavity
		Hiroshi Tsujioka and Toshihide Yamashita (Molecular Neuroscience)	Transcriptomic analysis of spinal cord of axonal sprouting-capable neonatal mice after central nervous system injury
39th	October 24, 2018	Floris van Eerdan and Daron Standley (Systems Immunology)	Structural modeling of lymphocyte receptors and their antigens
		Hisamichi Naito and Nobuyuki Takakura (Signal Transduction)	The role of endothelial stem cells in vascular regeneration
		Masahiro Nagata and Sho Yamasaki (Molecular Immunology)	Identification of unique bacterial steroids that promote deleterious inflammation
40th	December 19, 2018	Ben Seymour and Toshio Yanagida (Single Molecule Imaging)	Integrated physiological systems for defence against injury
		Shimpei Kawamoto and Eiji Hara (Aging Biology)	The roles and mechanisms of cellular senescence in aging and cancer
		Tetsuya Kimura and Masato Okada (Oncogene Research)	Prevention of Obesity by Macrophages

Science Café

The series of science cafes is a long-standing IFReC outreach activity to promote communication between researchers and the general public. It also enhances people's understanding of immunology researches and the researchers involved . In the two science cafés organized by IFReC in FY2018, about 150 participants in total enjoyed novel topics in immunology in a relaxing atmosphere.

Science Café on the Edge at Icho Festival 2018

< IGD causes epilepsy and growth delay >

- Speaker : Yoshiko Murakami (Professor, Immunoglycobiology, IFReC/RIMD)
- Date : April 30, 2018
- Venue : TechnoAlliance Hall, Suita Campus, Osaka University

Science Café on the Edge at Nakanoshima Festival

< Brain tumor and immunity -Mystery of lymphocytes remaining in bone marrow- >

- Speaker : Shohei Koyama (Assistant Professor, Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University)
- Date : December 9, 2018
- Venue : Graduate School of Medicine, Osaka University

Students Visit

Thirty students visited IFReC on a tour organized by Nara High School, which is designated as a Super Science High School. After the lecture by Assist. Prof. Akiko Nakai (Immune Response Dynamics), the students toured the Laboratory of Host Defense and the Imaging Facility before trying experiments and talking with researchers. Responses from the participants include "a very valuable, unique, and exceptional experience."

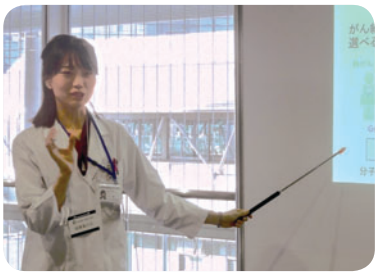
- **Date :** August 23, 2018



Science Agora

IFReC participated in Science Agora 2018 held in Tokyo. At the exhibition booth titled "Let's think about genomic medicine with the gene counselors," we organized the screening of an original video depicting the process of genetic counseling, and a question and answer session by guest counselors.

- **Date :** November 9-11, 2018
- **Venue :** Telecom Center, Odaiba, Tokyo




Osaka University Festival 2018

Co-Creation Festival 2018

IFReC participated in Osaka University Co-Creation Festival 2018 organized by the headquarters office of Osaka University. This event was called “Let's Have Fun with Osaka University!" In the event, IFReC demonstrated the observation of various immune cells through a microscope. Using videos and photos, we also introduced the research of IFReC. The venue was full of visitors throughout the day.

- **Date :** November 17, 2018
- **Venue :** LaLaport EXPOCITY, Suita

Workshop Festival at Grand Front Osaka

Knowledge Capital at GFO (Grand Front Osaka) has regularly held the workshop festival with the aim of utilizing Knowledge Capital as a learning place for students and kids. As part of the program, IFReC organized an event, which introduced immunity to children by making models of blood and immune cells.

- **Date :** March 16-17, 2019
- **Venue :** Grand Front Osaka

Super Science High School Student Fair

Super Science High Schools (SSH) are high schools designated by Japan's MEXT (Ministry of Education, Culture, Sports, Science and Technology), which promote advanced math/science education and collaborative research projects with universities as well as activities to develop international perspectives.

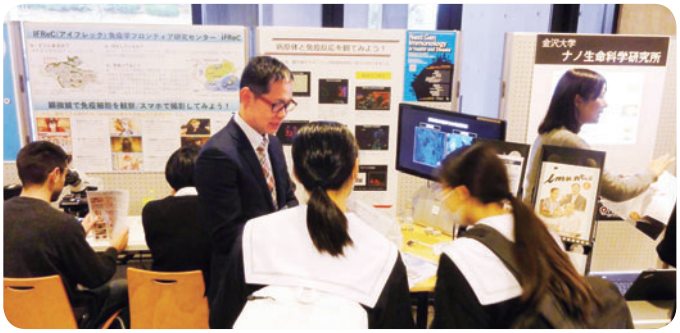
In the SSH Student Fair 2018, more than 200 schools, including over 10 schools from overseas, held booths with posters to present their research achievements. IFReC and other WPI institutes held a collaborative booth and introduced the research activities of each institute using posters, booklets, and demonstrations.

- **Date :** August 8-9, 2018
- **Venue :** Kobe International Exhibition Hall
- **Host :** MEXT and JST
- **Support :** Boards of Education (Hyogo prefecture and Kobe city)

"Kagaku Zanmai" in Aichi 2018

"Kagaku Zanmai (addiction to science)" is an advanced initiative called Aichi Model. In this program, the high schools in Aichi prefecture that are actively engaged in science education collaborate with universities and research institutes to conduct research and presentation. At the annual meeting of Kagaku Zanmai 2018, WPI institutes organized a presentation booth to demonstrate top level research in Japan.

- Date : December 27, 2018
- Venue : Toyota Auditorium, Nagoya University
- Host : Okazaki High-school, Aichi prefecture



The 7th WPI Science Symposium

ITbM and WPI institutes co-organized the 7th WPI Science Symposium in Nagoya. At the booth of IFReC, with the assistance of overseas students, we introduced images and videos obtained through IFReC research, and distributed leaflets of IFReC and WPI.

- Date : December 27, 2018
- Venue : Toyota Auditorium, Nagoya University
- Host : Institute of Transformative Bio-Molecules (WPI- ITbM), Nagoya University
- Support : Nagoya city, Aichi prefecture, MEXT

AAAS Annual Meeting 2019

The American Association for the Advancement of Science (AAAS), the publisher of Science journal, is the biggest international non-profit organization in the world, and its mission is to "advance science and serve society". The AAAS Annual Meeting assembles diverse participants, including scientists, families, science policymakers, and the media etc., offering symposia, lectures, seminars, poster presentations and exhibitions on a variety of scientific topics.

WPI institutes participated in the AAAS 2019 Annual Meeting in Washington D.C. We held a collaborative booth to introduce the WPI program and the institutes' activities including our approaches for interdisciplinary research and internationalization.

The next AAAS annual meeting will be held in Seattle, WA, USA on Feb. 13-16, 2020.

- **Date :** February 14-17, 2019
- **Venue :** Hotel Marriott Wardman Park DC, Washington, D.C., USA
- **Host :** American Association for the Advancement of Science

Japanese Language Classes

Japanese language classes are held for overseas researchers / students to alleviate any stress and inconvenience in research or daily life that may be caused by the language barrier.

We offer two lecture-style classes, "Class A: Elementary to Pre-intermediate" and "Class B: Intermediate to Advanced." Students are expected to learn basic Japanese grammar including verb and adjective conjugations in Class A, and to learn intermediate/advanced level grammar and vocabulary to improve upon what was learned in Class A as well as kanji in Class B.

The instructor of our Japanese class, Ms. Tajima, who has greatly contributed to our Japanese Class since it launched in 2012, has finished teaching at IFReC. A new instructor, Ms. Tomomune, has succeeded her from FY 2019.

It has been a great pleasure to work with the researchers at IFReC. They were always highly motivated to learn new Japanese grammar and vocabulary despite their busy work schedules. During the lessons, they tried hard to use as much Japanese as possible in discussing their daily lives. As a result, they learned many expressions which were not even in the textbook. Tuesdays and Thursdays have been my favorite days of the week. I will miss them a lot.

Kaori Tajima

I have been teaching Japanese in Japan and the USA to international students from all over the world. In my teaching experience, I am always striving to make my class more interactive so that students can learn independently among themselves, and I also try to have my students experience Japanese customs and culture in my class through hands-on activities such as writing new year greeting cards and introducing Japanese seasonal events. I am also striving to have students develop their communication skills that are essential for daily life in Japan. Going shopping, speaking with classmates, and making friends in Japanese will make their lives more enjoyable.

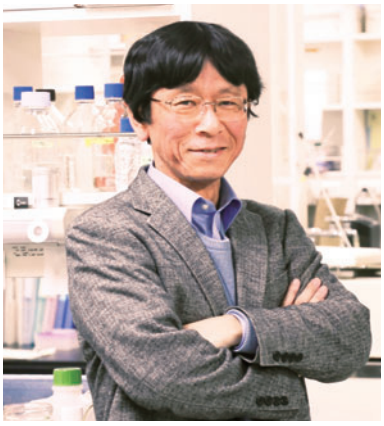
Tomomi Tomomune

Major Awards

Takashi Nagasawa　Japan Academy Prize

Takashi Nagasawa (Stem Cell Biology and Developmental Immunology, IFReC/Graduate School of Frontier Biosciences, Osaka University) won the Japan Academy Prize. The awarded title is “Elucidation of Microenvironments Essential for the Maintenance of Hematopoietic Stem Cells, Hematopoiesis and Bone”.

Taroh Kinoshita　Medal with Purple Ribbon



Taroh Kinoshita (Immunoglycobiology, IFReC/RIMD) won the Medal with Purple Ribbon, which is awarded to people who have made outstanding contributions in academic fields, arts and sports. Kinoshita and his research group have been trying to reveal how GPI-anchored proteins are synthesized, processed, transported and secreted, and how defects in these processes lead to the onset and pathology of diseases. They have made considerable achievements in this field.

Kazuya Kikuchi and Miwa Sasai　MEXT Scientists' Prize

Kazuya Kikuchi (Chemical Imaging Techniques, IFReC/Graduate School of Engineering) was awarded by the Minister of Education, Culture, Sports, Science and Technology (MEXT) for his outstanding achievement in "Developments of chemical probes to visualize the functions of the cells and the molecules in living animals". Miwa Sasai (Immunoparasitology, IFReC/RIMD) was given the Young Scientists' Prize of the Commendation for Science and Technology by MEXT. She was awarded for her study on "Pathogen elimination mechanism via intracellular endoplasmic reticulum transport".

Sho Yamasaki and Sujin Kang　Awarded by JSI

Sho Yamasaki (Molecular Immunology, IFReC/RIMD) won the Japanese Society for Immunology (JSI) Award 2018 for his outstanding achievements in the studies of "mechanisms of pathogen recognition by immune receptors". Sujin Kang (Immune Regulation, IFReC) won the JSI Young Investigator Award 2018. She was recognized for her achievements in immune semaphorins, which involve linking immunity and lipid metabolism.

Masahiro Yamamoto　Japan Medical R&D Grand Prize/JSPS Prize

Masahiro Yamamoto (Immunoparasitology, IFReC/RIMD) won the Japan Medical R&D Grand Prize. The government commented Yamamoto was awarded for his outstanding achievements in the studies of "the elucidation mechanism of host immune system against the pathogenic parasite infections". Using Toxoplasma infection as a model, his group has revealed the ingenious mechanism of the evolved host immune system. Yamamoto also won the JSPS Prize 2018 for his "Analysis of immunological interface between host and intracellular pathogens". A new treatment strategy by the cutting-edge parasitic immunology is widely expected in the world.

Osaka University and the three companies　Awarded by MEXT at JOIP

The Japan Open Innovation Prize (JOIP) was launched with the aim of appreciating the most leading and original initiatives expected to be used as future role models to further promote open innovations in Japan. In February, 2019, Osaka University, Chugai Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Daikin Industries, Ltd. won the MEXT Award at the 1st JOIP with "University-Industry Co-creation from the Basic Research Stage -Collaboration between Organizations". IFReC has greatly contributed to the contracts between Osaka Universisty and both pharmaceutical firms.

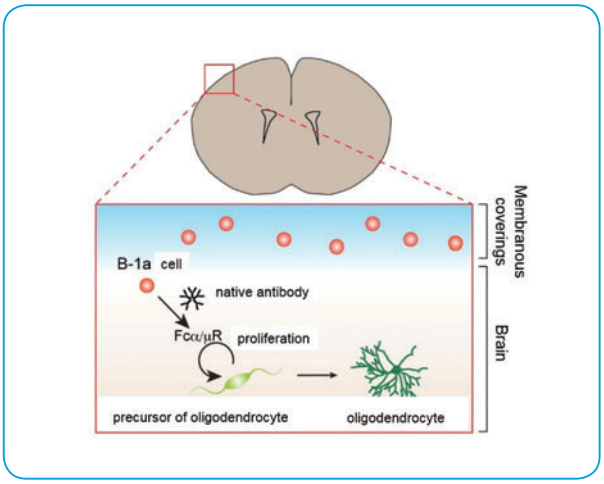
Selected Articles

B-1a lymphocytes promote oligodendrogenesis during brain development

Nature Neuroscience 21:506–516 (2018).

Tanabe S and Yamashita T.

Toshiihide Yamashita (Molecular Neuroscience, IFReC) and his research group identified the subtypes of lymphocytes that are present in neonatal mouse brains and investigated their functions. They found that B-1a cells, a subtype of B cells, were abundant in the neonatal mouse brain and infiltrated into the brain in a CXCL13–CXCR5-dependent manner. B-1a cells promoted the proliferation of oligodendrocyte-precursor cells (OPCs) in vitro, and depletion of B-1a cells from developing brains resulted in a reduction of numbers of OPCs and mature oligodendrocytes. Furthermore, neutralizing Fcα/μR, the receptor for the Fc region of IgM secreted by B-1a cells, inhibited OPC proliferation and reduced the proportion of myelinated axons in neonatal mouse brains. These results demonstrate that B-1a cells infiltrate into the brain and contribute to oligodendrogenesis and myelination by promoting OPC proliferation via IgM–Fcα/μR signaling.



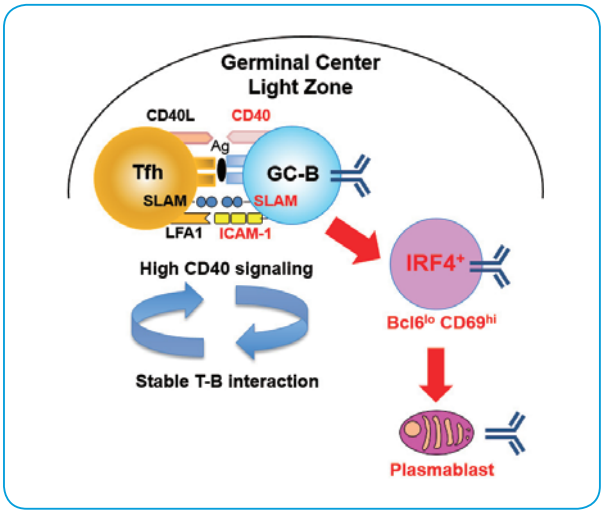
Immunity. 48:702-715 (2018).

T follicular helper cell-germinal center B cell interaction strength regulates entry into plasma cell or recycling GC cell fate

Immunity 48:702-715 (2018).

Ise W, Fujii K, Shiroguchi K, et al.

Wataru Ise, Tomohiro Kurosaki (Lymphocyte Differentiation, IFReC) and the research group discovered how high affinity antibodies, which are essential for host protection from pathogens, are generated. The findings in this study are expected to contribute to the development of novel vaccine that targets efficient production of antibody against various virus. Using mouse model, the study clarified the cellular and molecular mechanism by which "high quality" antibodies, which have high affinity against pathogens such as influenza virus, are developed during immune response. Upon invasion of pathogens to our body, B cells are activated and differentiated to plasma cells which produce pathogen-specific antibodies. Importantly, some of activated B cells form germinal centers, microenvironments where B cells with high affinity antibodies are generated. Thus, germinal center B cells are sources of plasma cells producing high affinity antibodies. This study analyzed germinal center B cells carefully and identified plasma cell precursors among germinal center B cells. Furthermore, the study revealed what kind of signals or molecules are involved in the development of such plasma cell precursors in germinal center. Together, the efficient induction of plasma cell precursors in germinal center would be the one of the targets of new vaccine.

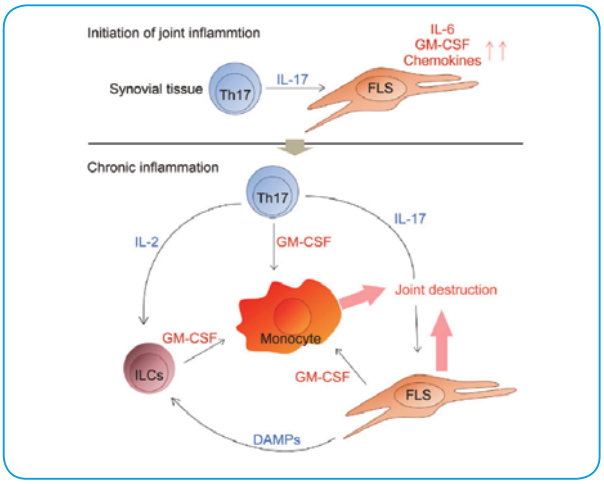


Autoimmune Th17 cells induced synovial stromal and innate lymphoid cell secretion of GM-CSF to initiate and augment autoimmune arthritis

Immunity 48:1220-1232.e5. (2018).

Hirota K, Hashimoto M, Yoshinaga I, et al.

Despite the importance of Th17 cells in autoimmune diseases, it remains unclear how they control other inflammatory cells in autoimmune tissue damage. Using a model of spontaneous autoimmune arthritis, Hirota and Sakaguchi's group (Experimental Immunology, IFReC) showed arthritogenic Th17 cells stimulated fibroblast-like synoviocytes via interleukin-17 (IL-17) to secrete the cytokine GM-CSF and also expanded synovial-resident innate lymphoid cells (ILCs) in inflamed joints. Activated synovial ILCs, which expressed CD25, IL33Ra, and TLR9, produced abundant GM-CSF upon stimulation by IL-2, IL-33, or CpG DNA. Loss of GM-CSF production by either ILCs or radio-resistant stroma cells prevented Th17 cell-mediated arthritis. GM-CSF production by Th17 cells augmented chronic inflammation but was dispensable for the initiation of arthritis. The authors showed GM-CSF-producing ILCs were present in inflamed joints of rheumatoid arthritis patients. Thus, a cellular cascade of autoimmune Th17 cells, ILCs, and stroma cells, via IL-17 and GM-CSF, mediates chronic joint inflammation and can be a target for therapeutic intervention.

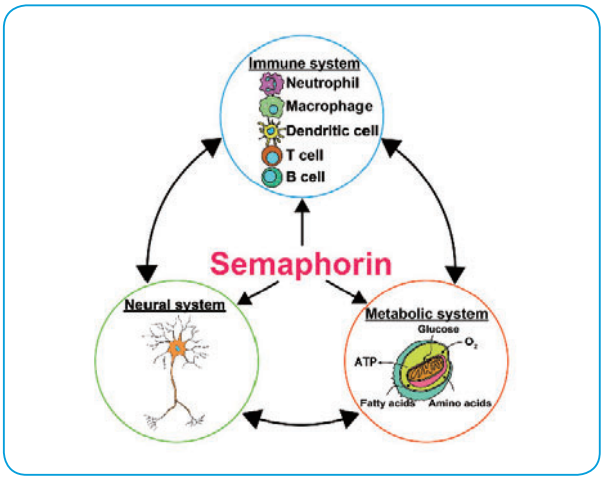


Semaphorin 6D reverse signaling controls macrophage lipid metabolism and anti-inflammatory polarization

Nature Immunology 19:561–570 (2018).

Kang S, Nakanishi Y, Kioi Y, et al.

Polarization of macrophages into pro-inflammatory or anti-inflammatory states has distinct metabolic requirements, with mechanistic target of rapamycin (mTOR) kinase signaling playing a critical role. However, it remains unclear how mTOR regulates metabolic status to promote polarization of these cells. Sujin Kang, Atsushi Kumanogoh (Immunopathology, IFReC) and the research group showed that an mTOR-Semaphorin 6D (Sema6D)-Peroxisome proliferator receptor γ (PPARγ) axis plays critical roles in macrophage polarization. Inhibition of mTOR or loss of Sema6D blocked anti-inflammatory macrophage polarization, concomitant with severe impairments in PPARγ expression, uptake of fatty acids, and lipid metabolic reprogramming. Macrophage expression of the receptor Plexin-A4 is responsible for Sema6D-mediated anti-inflammatory polarization. The group found that a tyrosine kinase, c-Abl, which associates with the cytoplasmic region of Sema6D, is required for PPARγ expression. Furthermore, Sema6D is important for generation of intestinal resident CX3CR1hi macrophages and prevents development of colitis. Collectively, these findings highlight crucial roles for Sema6D reverse signaling in macrophage polarization, coupling immunity, and metabolism via PPARγ.



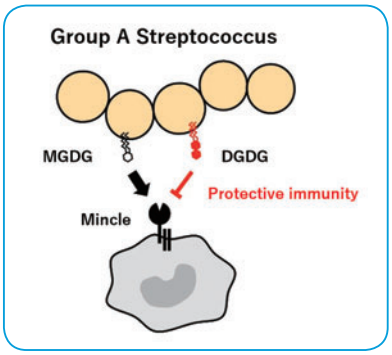
Lipoteichoic acid anchor triggers Mincle to drive protective immunity against invasive group A Streptococcus infection

Proc Natl Acad Sci USA 115:E10662-E10671 (2018).

Imai T, Matsumura T, Mayer-Lambertz S, et al.

Group A Streptococcus (GAS) causes invasive streptococcal infections in humans, resulting high mortality. Thus, GAS is also known as "killer bacteria" or "flesh-eating bacteria". However, the mechanisms by which the innate immune system recognizes GAS are not well understood.

Sho Yamasaki (Molecular Immunology, IFReC) and his research group reported that the C-type lectin receptor macrophage inducible C-type lectin (Mincle) recognizes GAS and initiates anti-bacterial immunity. Gene expression analysis of myeloid cells upon GAS stimulation revealed the contribution of the caspase recruitment domain-containing protein 9 (CARD9) pathway to the anti-bacterial responses. Among receptors signaling through CARD9, Mincle induced the production of inflammatory cytokines, inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS) upon recognition of the anchor of lipoteichoic acid (LTA), monoglucosyldiacylglycerol (MGDG), produced by GAS. Upon GAS infection, Mincle-deficient mice exhibited impaired production of pro-inflammatory cytokines, severe bacteremia and rapid lethality. GAS also possesses another Mincle ligand, diglucosyldiacylglycerol (DGDG); however, this glycolipid interfered with MGDG-induced activation. These results indicate that Mincle plays a central role in protective immunity against acute GAS infection.



Humanized cereblon mice revealed two distinct therapeutic pathways of immunomodulatory drugs

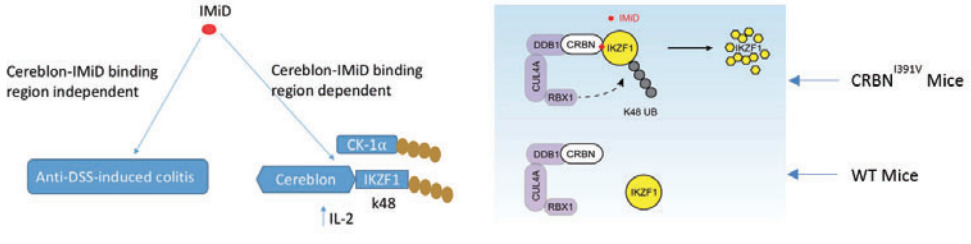
Proc Natl Acad Sci USA 115:11802-11807 (2018).

Gemechu Y, Millrine D, Hashimoto S, et al.

After its appearance on the drug market, it was found out that thalidomide was highly teratogenic. Although thalidomide passed the safety check in pregnant mice, it was not safe among humans due to different actions of thalidomide among various species. Due to inactivity of immunomodulatory drugs (IMiDs) in mice, preclinical safety checks and clinical investigation of IMiDs is impossible in murine models. Further, murine cereblon (CRBN), the substrate receptor for IMiD action, is resistant to some of IMiDs therapeutic effects.

To overcome this difficulty, the research group of Tadamitsu Kishimoto (Immune Regulation, IFReC) generated humanized cereblon (CRBNI391V) mice thereby providing an animal model to unravel complex mechanisms of action in a murine physiological setup. This model may also permit investigation of the main safety concerns.

The group found the degradative effect of IMiDs on IKZF1 and CK-1α, as well as upregulation of IL-2, is dependent on the CRBN-IMiD binding region. Therefore, the anti-inflammatory bowel disease benefit of IMiD is mediated through a CRBN–IMiD binding region-independent pathway.



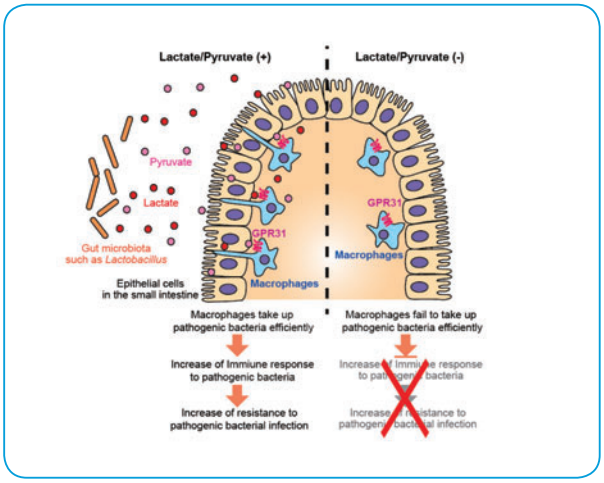
GPR31-dependent dendrite protrusion of intestinal CX3CR1+ cells by bacterial metabolites

Nature 566:110-114 (2019).

Morita N, Umemoto E, Fujita S, et al.

Eiji Umemoto, Naoki Morita, Kiyoshi Takeda (Mucosal Immunology, IFReC) and the research group showed common bacterial metabolites pyruvate and lactate enhance the intestinal immune response and guard against infection by important gut pathogens.

Gut microbiota such as lactobacillus produce lactate and pyruvate. These metabolites stimulate intestinal macrophages through the receptor GPR31, allowing macrophages to protrude trans-epithelial dendrites and take up pathogenic bacteria efficiently in the intestine. Accordingly, lactate and pyruvate cause enhanced immune responses to pathogenic bacteria and increased resistance to the infection.

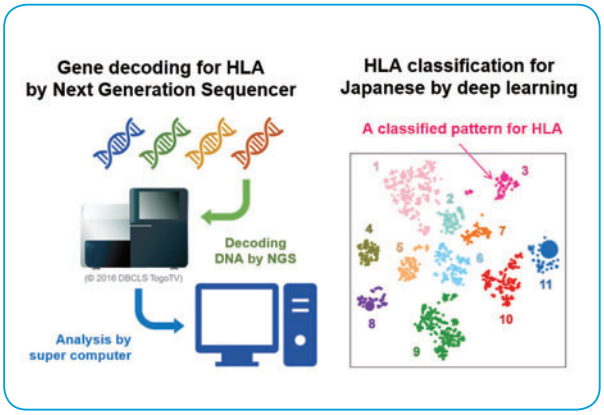


Genetic and phenotypic landscape of the MHC region in the Japanese population

Nature Genetics 51:470-480 (2019).

Hirata J, Hosomichi K, Sakaue S, et al.

Yukinori Okada (Statistical Immunology, IFReC) and the research group conducted NGS-based typing of the 33 human leukocyte antigen (HLA) genes of 1,120 Japanese, providing high resolution allele catalogue and linkage disequilibrium (LD) structure of both classical and non-classical HLA genes. Together with population-specific deep whole-genome sequencing (WGS) data (n = 1,276), they conducted NGS-based HLA, SNV, and indel imputation of large-scale genome-wide association (GWAS) data of 166,190 Japanese. A phenome-wide association study (PheWAS) assessing 106 clinical phenotypes identified abundant significant genotype-phenotype associations across 52 phenotypes. Fine-mapping highlighted multiple association patterns conferring independent risks from the classical HLA genes. Region-wide heritability estimates and genetic correlation network analysis elucidated polygenic architecture shared across the phenotypes.



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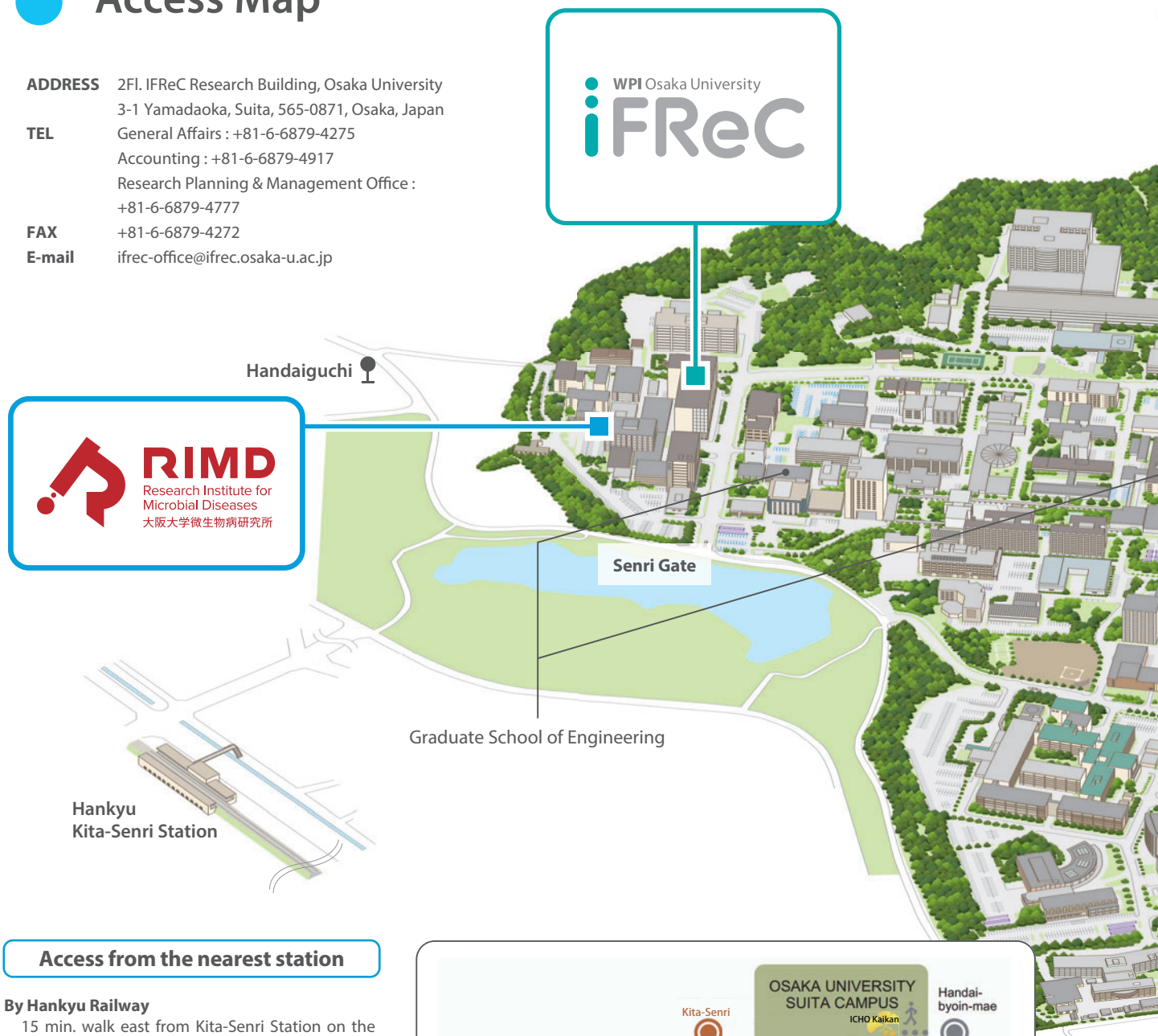

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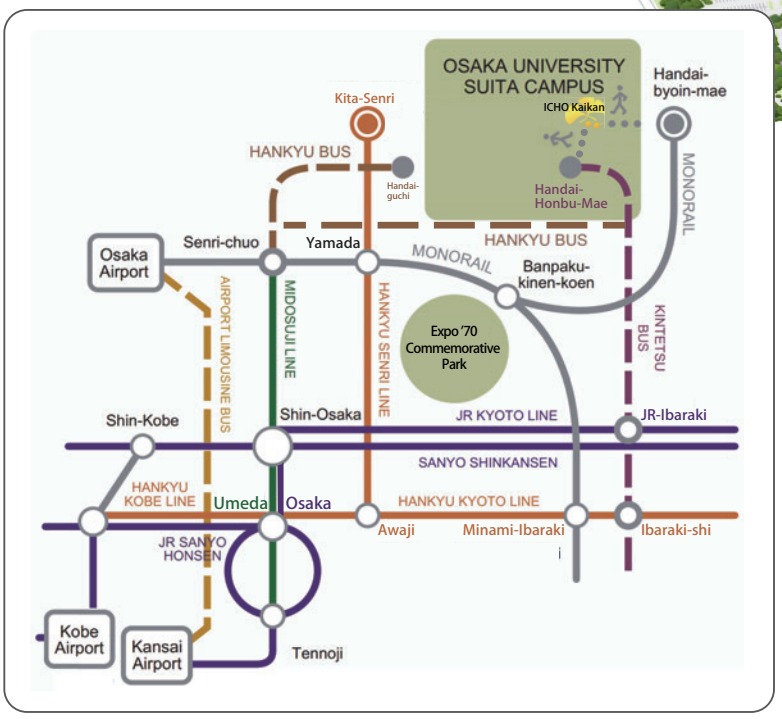

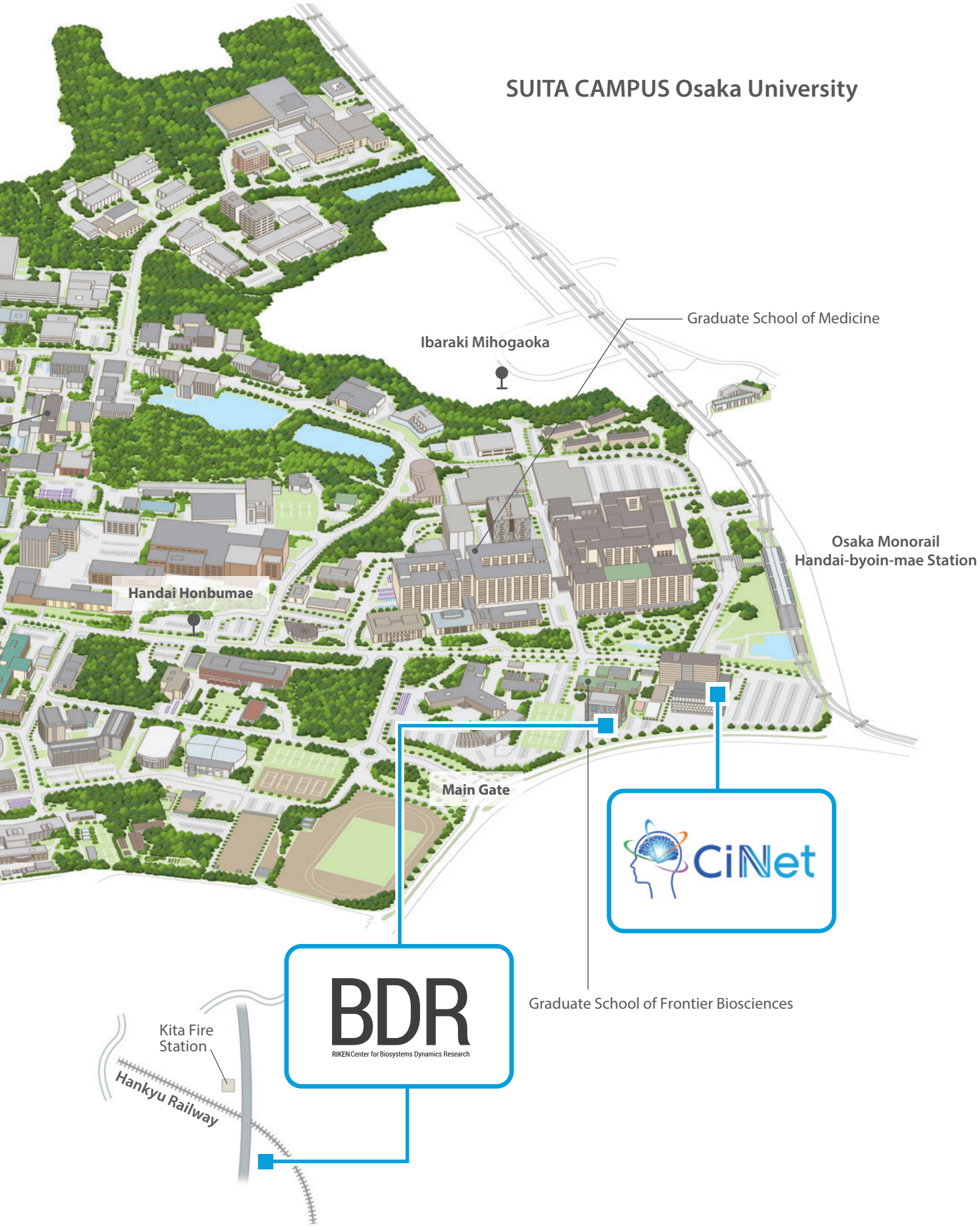
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