

Osaka University

# RIMD

Research Institute for Microbial Diseases

2017-2018



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Osaka University RIMD Research Institute for Microbial Diseases

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for Microbial Diseases



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## Research Institute for Microbial Diseases, Osaka University

Research Institute for Microbial Diseases (RIMD), Osaka University is a world's foremost institute for basic biological researches including microbiology, immunology and oncology.

We dedicate to stimulate fundamental biological researches as a MEXT Joint usage/research center.





# Message from the Director

In 1934, the Research Institute for Microbial Diseases (RIMD), the first institute attached to Osaka University, was established for the study of microbial diseases. For more than 80 years since its foundation, the RIMD has concentrated on basic researches in infectious diseases, immunology, and oncology and made significant contributions to the control of infectious diseases through the identification of new pathogens, the elucidation of pathogenesis of microbes, and the

development of vaccines and diagnostics based on these basic research findings. In addition, the RIMD has achieved an outstanding contribution in the progress of life sciences through the discovery of oncogenes and cell fusion phenomena and the elucidation of innate immune system.

The RIMD is certified as the Joint Usage/ Research Center by the Ministry of Education, Culture, Sports, Science and Technology Japan (MEXT). In addition to the collaborative research conducting in our facilities, the RIMD is also responsible to support for international scientific community through the provision of the bacteria stored at our Pathogenic Microbes Repository Unit. Faculties at the RIMD are also affiliated to the Graduate Schools of Medicine, Frontier Biosciences, Science, and Pharmaceutical Sciences at Osaka University and accepted many graduate students worldwide for contribution to the development of human resource in the next generations.

*Y. Matsuura*

Yoshiharu Matsuura D.V.M., Ph.D.  
Director  
Research Institute for Microbial Diseases  
Osaka University

The RIMD produces world-leading research on infectious diseases from basic research to clinical applications through tight collaborations with BIKEN, public interest incorporated foundation engaged in development, production and supply of a wide variety of vaccines based on the research findings in the RIMD, and the Immunology Frontier Research Center (IFReC), established by the great efforts of 4 researchers in the RIMD to develop new research projects designed to clarify immune responses in a spatio-temporal manner in the body.

The RIMD will continue to dedicate our efforts in the progress of the basic research of infectious diseases, immunology, oncology, developmental biology, and cell biology based on the past outstanding achievements, and to focus on the development of young researchers either in Japan or abroad who are highly motivated to discover and establish new scientific paradigms by themselves.

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# Organization

## Research Divisions

### To explore the pathogenesis of microbes Division of Infectious Disease

- Dept. of Molecular Bacteriology  
Horiguchi Lab
- Dept. of Viral Infections  
Shioda Lab
- Dept. of Molecular Virology  
Matsuura Lab
- Dept. of Infection Microbiology  
Mimuro Lab
- Dept. of Immunoparasitology  
Yamamoto Lab

### To explore the mechanisms that protect against microbes Division of Host Defense

- Dept. of Molecular Immunology  
Yamasaki Lab
- Dept. of Host Defense  
Akira Lab
- Dept. of Immunochimistry  
Arase Lab

### To explore regulatory mechanisms in cancer cells Division of Cellular and Molecular Biology

- Dept. of Molecular Microbiology  
Hara Lab
- Dept. of Oncogene Research  
Okada Lab
- Dept. of Signal Transduction  
Takakura Lab
- Dept. of Cellular Regulation  
Miki Lab

## Office of Combined Program on Microbiology and Immunology

## Common Research Facilities

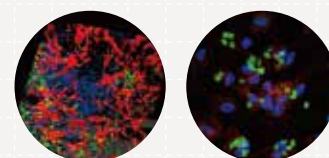
- Central Laboratory for Biological Hazardous Microbes
- Central Instrumentation Laboratory
- Radioisotope Laboratory

# RIMD

Research Institute for Microbial Diseases,  
Osaka University

Research Institute for Microbial Diseases (RIMD) was established as a research center for microbiology, immunology and oncology in 1934. We have performed outstanding researches in these fields and we also contribute extensively to growth in the

basic sciences in Japan through advanced research and the development of human resources. Now, we are also developing new research fields such as gene engineering, genome research and always exploring breakthrough in biological science.



## Special Research Facilities

### To overcome infectious diseases Research Center for Infectious Disease Control

- Dept. of Bacterial Infections  
Iida Lab
- Dept. of Molecular Protozoology  
Horii Lab
- Dept. of Virology  
Kobayashi Lab

### To understand our body system from genetic information Genome Information Research Center

- Dept. of Experimental Genome Research  
Ikawa Lab
- Dept. of Genome Informatics  
Daron Lab
- Dept. of Infection Metagenomics  
Horii Lab
- Next-Generation Sequencing (NGS) Core Facility

### To develop new therapeutic approaches to infectious diseases International Research Center for Infectious Diseases

- Lab. of Clinical Research on Infectious Diseases  
Kamitani Lab
- Lab. of Pathogen Detection and Identification  
Nakamura Lab
- Pathogenic Microbes Repository Unit

## Animal Resource Center for Infectious Diseases

### Research Collaboration Center for Infectious Diseases

- Section of Bacterial Infections
- Section of Viral Infections
- Section of Bacterial Drug Resistance Research
- Section of Antiviral Research

Mahidol-Osaka Center for Infectious Diseases

## Yabumoto Department of Intractable Disease Research

### To develop novel vaccines with high safety and efficacy BIKEN Innovative Vaccine Research Alliance Laboratories

- Vaccine Creation Project  
Yoshioka Lab
- Mucosal Vaccine Project  
Sato Lab
- Vaccine Dynamics Project  
Aoshi Lab



Some pathogenic bacteria cause specific disease symptoms including flaccid/spastic paralyses, paroxysmal coughing, skin exfoliation, and osteogenesis imperfecta, besides general symptoms such as fever and inflammation. Our major questions are as to how these specific symptoms appear in response to bacterial infections or what kinds of bacterial virulence factors are involved in them. We hope that we will understand the nature of bacterial infections by answering these questions.

### Professor Yasuhiko Horiguchi

#### Profile

Dr. Horiguchi received his Ph.D. from Osaka Prefecture University in 1987. After working at the Kitasato Institute for 3 years, he has worked for RIMD since 1990. He took his position as Postdoc in 1990, a Research Associate in 1992, an Associate Professor in 1998. He was appointed current position in 2001.



#### Publication

- (1) The bvg-repressed gene brtA, encoding biofilm-associated surface adhesin, is expressed during host infection by *Bordetella bronchiseptica*. Nishikawa S., et al. *Microbiol Immunol* (2016) 60: 93-105.
- (2) Polymorphisms Influencing Expression of Dermonecrotic Toxin in *Bordetella bronchiseptica*. Okada K., et al. *PLoS ONE* (2015) 10:e0116604.
- (3) Swine Atrophic Rhinitis Caused by *Pasteurella multocida* Toxin and *Bordetella* Dermonecrotic Toxin. Horiguchi Y. *Curr Topics Microbiol Immunol* (2012) 361:113-29
- (4) Crystal structure of *Clostridium perfringens* enterotoxin displays features of beta-pore-forming toxins. Kitadokoro K., et al. *J Biol Chem* (2011) 286:19549-55.
- (5) Characterization of the membrane-targeting C1 domain in *Pasteurella multocida* toxin. Kamitani S., et al. *J Biol Chem* (2010) 285:25467-75.
- (6) *Clostridium perfringens* enterotoxin interacts with claudins via electrostatic attraction. Kimura J., et al. *J Biol Chem* (2010) 285:401-8.

### To understand the mechanism of infection

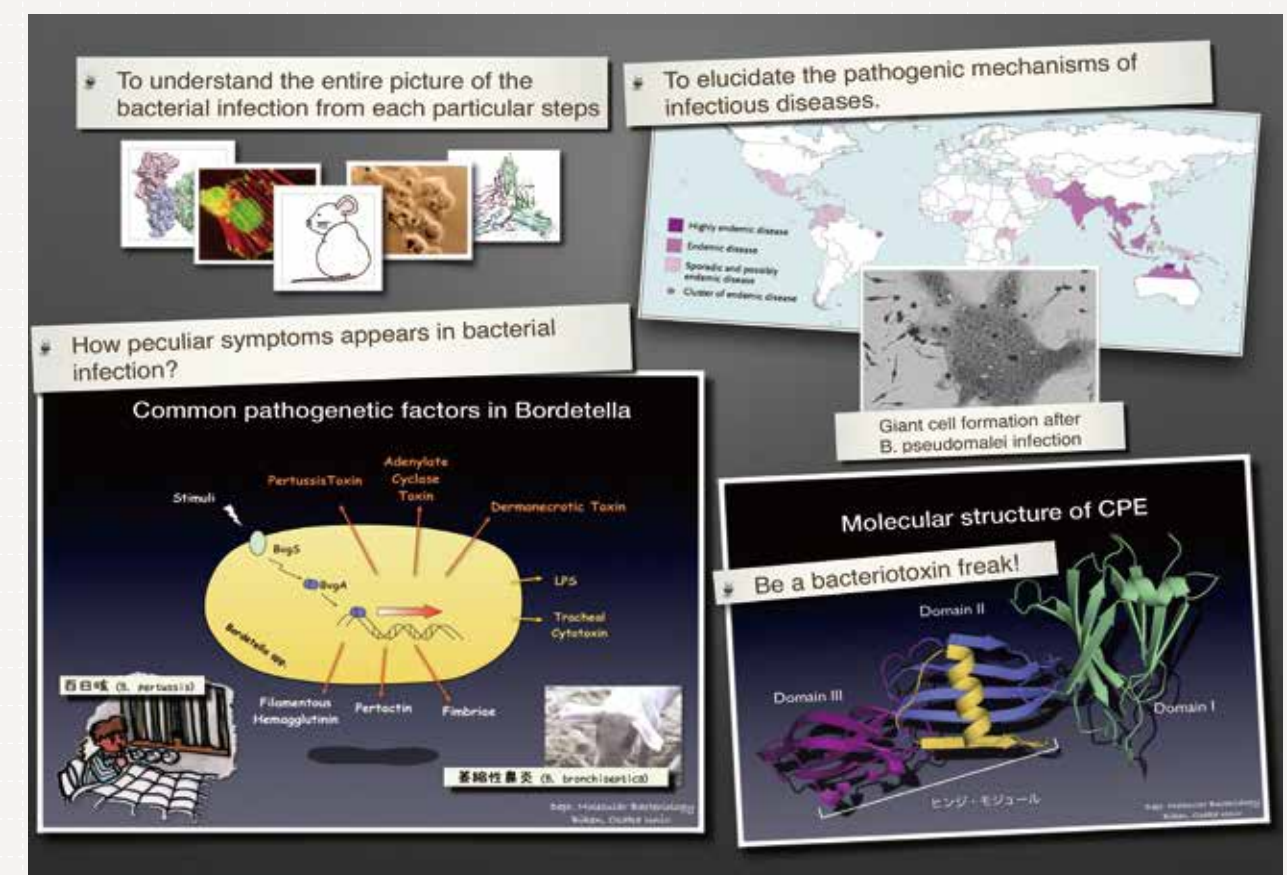
*Bordetella pertussis*, which is one of our research subjects is a representative pathogenic bacteria of *Bordetella* and causes whooping cough. In addition to *B. pertussis*, *B. parapertussis* and *B. bronchiseptica* are categorized in the genus *Bordetella*. Although these pathogenic organisms share homologous virulence factors and commonly cause respiratory infections with characteristic coughing, their host specificities and the course of disease manifestation are quite different: *B. pertussis* is a strict human pathogen causing the acute disease whereas *B. bronchiseptica* infects a wide range of mammals and causes chronic infections. We are trying to understand what determines host specificities and distinct disease manifestations in *Bordetella* infections. Understanding the molecular mechanism by which the bacteria cause coughing in hosts is our another goal of the *Bordetella* research.

We are also studying on virulence factors of *Burkholderia pseudomallei*, which causes melioidosis, an endemic disease in Southeast Asia, northern Australia, and so on.

### Analyzing the structure-function relationship of bacterial protein toxins.

Bacterial protein toxins cause a variety of specific symptoms manifested in bacterial infections. Many bacterial protein toxins are essentially multifunctional biomolecules, which travel in a host body, bind to target molecules or cells, and modify target molecules with high specificity. Some bacterial toxins are known as the most poisonous substances on the earth. We are analyzing the structure-function relationship of these bacterial protein toxins to understand how they exert such powerful toxicities on target cells and intoxicated animals. We believe that these results should give an insight into the mechanism causing specific symptoms observed in bacterial infections.

To achieve the above-mentioned goals, we are conducting the research work by using every experimental technique based on bacteriology, molecular and cellular biology, biochemistry, medical and veterinary science.



### Staff

Asst. Prof. : Naoaki Shinzawa / Asst. Prof. : Yukihiro Hiramatsu /  
Postdoc. : Noriko Shinoda / Grad. Student 5



Viruses are simple organisms composed of proteins, nucleic acids, and, in some cases, lipids. Nevertheless, they interact with several host factors and ultimately cause disease in humans. Our laboratory focuses on the molecular mechanisms underlying viral diseases, including human immunodeficiency virus (HIV).

### Professor Tatsuo Shioda

#### Profile

Dr. Shioda obtained his B. Sc. from the University of Tokyo in 1982 and his Ph.D. from the same institution in 1990. After working at the Institute of Medical Science in the University of Tokyo and University of California San Francisco, he was appointed as Associate Professor in 1997. He took his current position as a Professor of RIMD in 2000.



#### Publication

- (1) A naturally occurring single amino acid substitution in human TRIM5α linker region affects its anti-HIV-1 activity and susceptibility to HIV-1 infection. Nakayama E.E., et al. *AIDS Res Hum Retroviruses*. (2013) 29(6):919-24.
- (2) Properties of human immunodeficiency virus type 1 reverse transcriptase recombination upon infection. Sakuragi S., et al. *J Gen Virol*. (2015) Nov;96(11):3382-8.
- (3) Genome-wide association study of HIV-related lipodystrophy in Thai patients: Association of a DLGAP1 polymorphism with fat loss. Uttayamakul S., et al. *AIDS Res Hum Retroviruses*. (2015) Aug;31(8):792-6.
- (4) Impact of TRIM5α in vivo. Nakayama E.E., et al. *AIDS*. (2015) Sep 10;29(14):1733-43.
- (5) A Single-Nucleotide Polymorphism in ABCG4 Is Associated with Tenofovir-Related Beta2-Microglobulinuria in Thai Patients with HIV-1 Infection. Likansakul S., et al. *PLoS One* (2016) Jan 25;11(1):e0147724.
- (6) Novel mutant human immunodeficiency virus type 1 strains with high degree of resistance to cynomolgus macaque TRIMCyp generated by random mutagenesis. Sultana T., et al. *J Gen Virol*. (2016) Apr;97(4):963-76.

### Antiviral host factors and their application to a cure for HIV infection

HIV does not establish a productive infection in any monkey other than the chimpanzee. Also, the sensitivity of HIV infection and rate of disease progression vary from individual to individual. To date, several anti-HIV host restriction factors, including TRIM5α and TRIMCyp, have been identified as responsible for these phenomena. Currently, we are trying to elucidate the molecular mechanism(s) underlying the anti-HIV activity of these factors. We also aim to cure HIV infection by establishing novel reproductive medicine-based strategies, including iPS cells from HIV patients.

### Analysis of HIV-1 genome RNA dimerization

The genome of retroviruses such as HIV-1 always exists as a dimer; genome dimerization plays an important role at various stages of the viral life cycle, including genome packaging and reverse transcription as well as the genome recombination processes involved in viral diversification. Therefore, genome dimerization is a novel target for anti-HIV therapies. We are currently analyzing computer-assisted structural models of HIV-1 Dimer Initiation Sequences, which are the most important factors involved in genome dimerization, to get a more complete picture of HIV genome dimerization. We are also analyzing genome recombination in HIV-1 by constructing a novel system to measure recombination efficiency.

### Human genome analysis of HIV-associated neurocognitive disorders

Despite successful antiretroviral therapy, nearly a quarter of HIV patients develop mild-to-severe neurocognitive disorders (HAND). We aim to undertake genome analysis of HAND patients to elucidate the underlying molecular mechanisms, thereby developing therapeutic strategies to treat/prevent this disease.

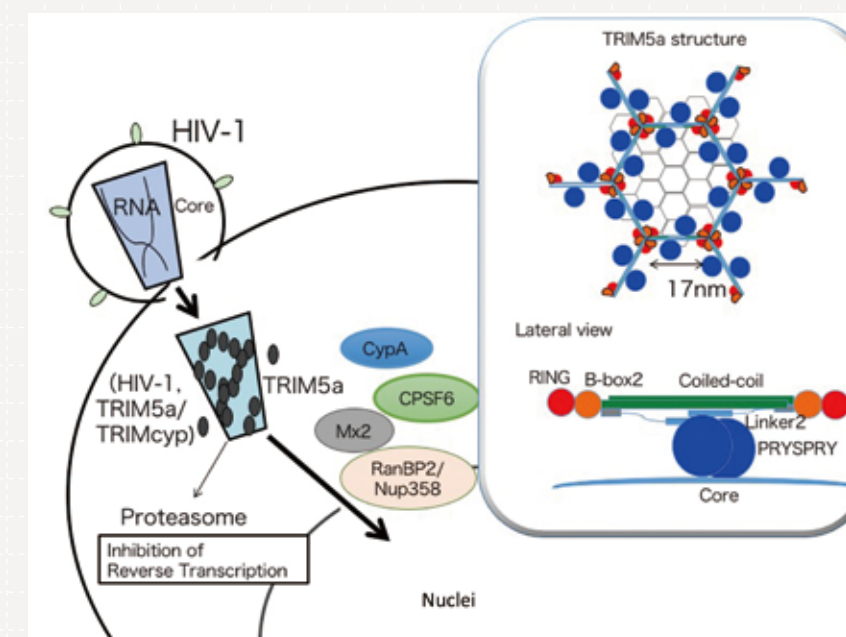


Fig. 1. Host factors involving in early replication steps of HIV

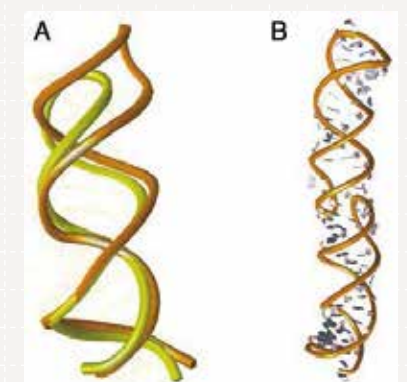


Fig. 2. Newly identified structure of DIS. A. Comparison of the current model (brown) with the previously proposed model (yellow). B. Structure in a dimeric form. The newly identified model shows more extended DIS structure possibly allowing stronger molecular interaction.

### Staff

Assoc. Prof. : Emi E. Nakayama /  
Asst. Prof. : Jun-ichi Sakuragi / Undergrad. Student 1

Viruses “know” cells better than human beings and have evolved to replicate in living cells. We are working to understand the molecular mechanisms underlying the interplay between viruses and host cells through research on hepatitis viruses, flaviviruses, and insect viruses.

## Professor Yoshiharu Matsuura

### Profile

Dr. Matsuura received his PhD from Hokkaido University in 1986 and worked at Research Institute of Daiichi Seiyaku Co. Ltd for . He was appointed Professor in RIMD in 2000 after working at NERC Institute of Virology in Oxford University as a postdoctoral fellow and at the National Institute of Infectious Diseases as a head of Laboratory of Hepatitis Viruses in Department of Virology II. He serves as Director of RIMD from 2015.



### Publication

- (1) TRC8-dependent degradation of hepatitis C virus immature core protein regulates viral propagation and pathogenesis. Aizawa S. & Okamoto T., et al. *Nat. Commun.* (2016), doi: 10.1038/ncomms11379.
- (2) Lipoprotein receptors redundantly participate in entry of hepatitis C virus Yamamoto S. & Fukuhara T., et al. *PLoS Pathog.* (2016), doi: 10.1371/journal.ppat.1005610.
- (3) Amphipathic  $\alpha$ -Helices in apolipoproteins are crucial to the formation of infectious hepatitis C virus particles. Fukuhara T., et al. *PLoS Pathogens* (2014), doi: 10.1371/journal.ppat.1004534.
- (4) Biological and immunological characteristics of hepatitis E virus-like particles based on the crystal structure. Yamashita T. & Mori Y., et al. *PNAS* (2009) 106:12986-91.
- (5) Critical role of PA28 $\gamma$  in hepatitis C virus-associated steatogenesis and hepatocarcinogenesis. Moriishi K., et al. *PNAS*, (2007) 104:1661-6.
- (6) Hepatitis C virus RNA replication is regulated by FKBP8 and Hsp90. Okamoto T., et al. *EMBO J.* (2006) 25: 5015-25.

### Staff

Assoc. Prof. : Yusuke Maeda / Asst. Prof. : Takasuke Fukuhara /  
Asst. Prof. : Toru Okamoto / Postdoc. : Chikako Ono /  
JSPS Postdoc. : Tomokazu Tamura / Undergrad. Student 1 / Grad. Student 8

## Molecular biology of hepatitis viruses

Hepatitis C virus (HCV) infects over 170 million individuals worldwide and is one of the most common etiologic agents of chronic liver disease, including liver cirrhosis and hepatocellular carcinoma (HCC). Although novel innovative anti-HCV drugs that act directly on viral proteins have achieved a sustained virological response in hepatitis C patients, drug-resistant viruses emerge easily. Therefore, host factors necessary for HCV replication are ideal targets for the development of new therapeutics for chronic hepatitis C; such drugs will lessen the possibility of drug-resistant breakthrough viruses emerging because the frequency of mutation is much lower than that in the viral genome.

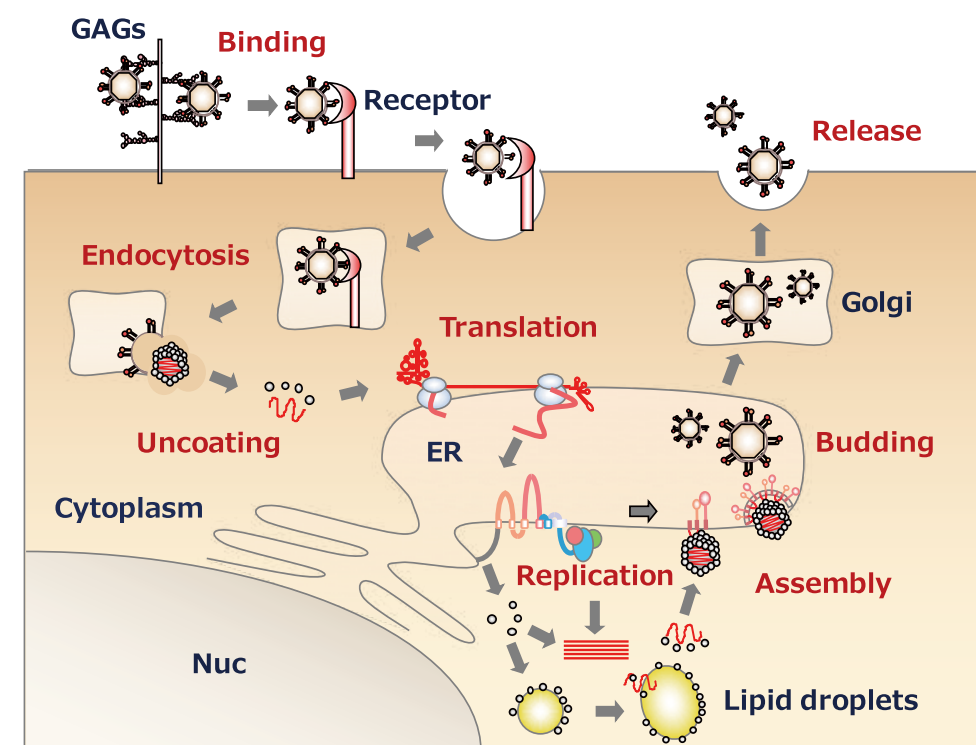
Upon infection with HCV, viral RNA is directly translated into viral proteins. Viral RNA replicates in the cytoplasm using various host factors and organelles. Viruses replicate in living cells, and some of them, including HCV, are pathogenic to the host. We are focusing on trying to understand the molecular mechanisms underlying the interaction between the virus and host by identifying the host factors involved in the propagation and pathogenicity of HCV. We have shown that the HCV core protein participates not only in the assembly of viral particles but also in the development of liver steatosis

and HCC. We have also shown that host proteins, including molecular chaperones and apolipoproteins, participate in viral replication and in the formation of infectious particles. Novel therapeutic agents targeting the host factors crucial for propagation and pathogenesis of HCV could be available if we can elucidate the molecular mechanisms underlying infection and replication of HCV. We are also working on hepatitis B virus and Japanese encephalitis virus, also members of the *Flaviviridae*.

## Development of baculoviral vectors

Development of viral vectors capable of safely transducing foreign genes into target cells is essential for future gene therapy. We are working on developing the insect baculovirus, *Autographa californica* nucleopolyhedro virus, as a versatile viral vector for gene delivery. Baculovirus is capable of entering a variety of mammalian cells and facilitates expression of foreign genes under the control of mammalian promoters; however, the viral genome does not replicate. We are working on developing viral vectors that have the advantages and characteristics of baculovirus.

## HCV life cycle



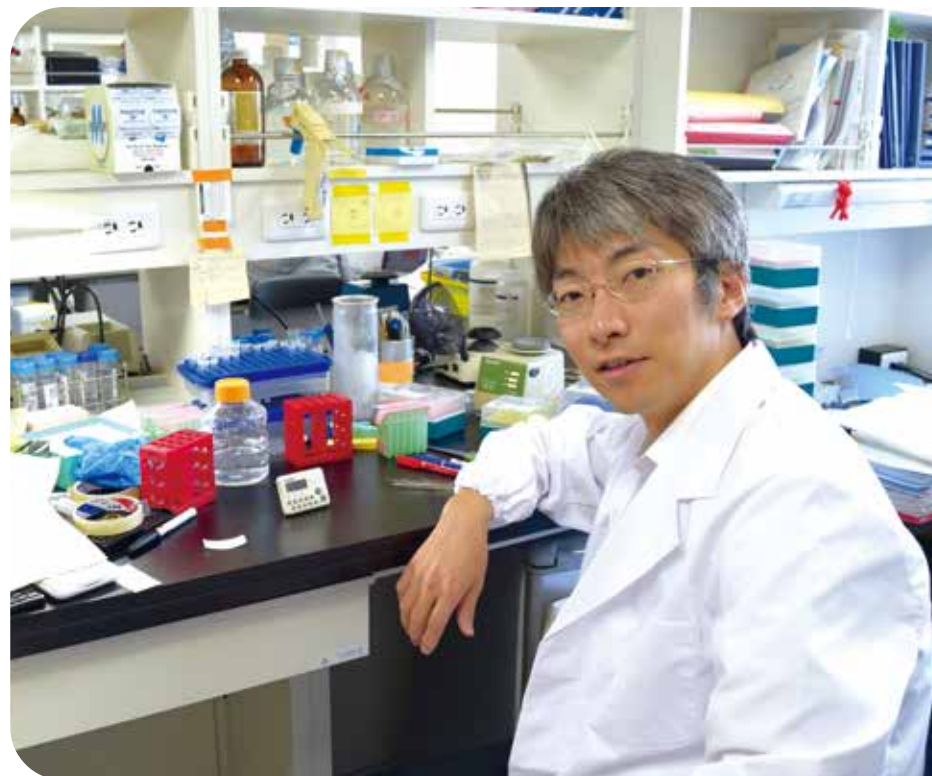


In our immunoparasitology laboratory, we use the apicomplex-an protozoan parasite *Toxoplasma gondii* as a model for exploring host defense systems and pathogenesis. Our research goal is to elucidate the molecular mechanisms underlying the interface between the host and pathogen.

### Professor Masahiro Yamamoto

#### Profile

Born at Kumamoto (1979). Received B. Sc. from the University of Tokyo (2001) and Ph.D. from Osaka University (2006). Promoted to an assistant professor (2006), an associate professor (2010) at the graduate school of medicine in Osaka University, an independent associate professor (2012) at RIMD in Osaka University. Appointed current position as a Professor of RIMD in 2013.



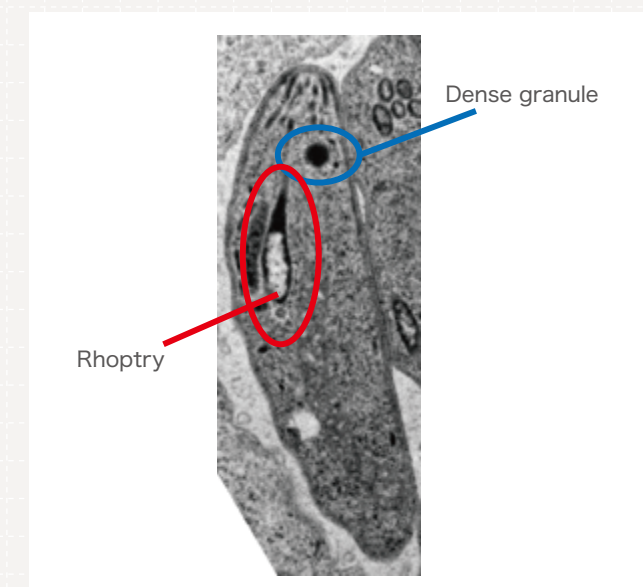
#### Publication

- (1) p62 plays a specific role in interferon- $\gamma$ -induced presentation of a *Toxoplasma* vacuolar antigen. Lee Y., et al. *Cell Rep.* (2015) 13:223-33.
- (2) RabGDIa is a negative regulator of interferon- $\gamma$ -inducible GTPase-dependent cell-autonomous immunity to *Toxoplasma gondii*. Ohshima J., et al. *Proc Natl Acad Sci USA.* (2015) 112:E4581-90.
- (3) Selective and strain-specific NFAT4 activation by the *Toxoplasma gondii* polymorphic dense granule protein GRA6. Ma J.S., et al. *J Exp Med.* (2014) 211:2013-32.
- (4) Role of the mouse and human autophagy proteins in IFN- $\gamma$ -induced cell-autonomous responses against *Toxoplasma gondii*. Ohshima J., et al. *J Immunol.* (2014) 192: 3328-35.
- (5) A cluster of interferon- $\gamma$ -inducible p65 GTPases plays a critical role in host defense against *Toxoplasma gondii*. Yamamoto M., et al. *Immunity* (2012) 37:302-13.
- (6) ATF6 $\beta$  is a host cellular target of the *Toxoplasma gondii* virulence factor ROP18. Yamamoto M., et al. *J Exp Med.* (2011) 208:1533-46.

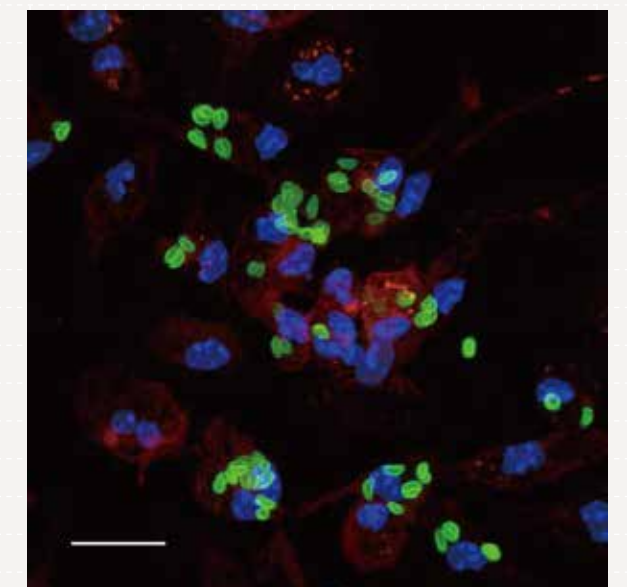
### Antiviral host factors and their application to a cure for HIV infection

*Toxoplasma gondii* is an obligatory intracellular protozoan pathogen that causes lethal toxoplasmosis in humans and animals. One third of the global population is thought to be infected with this pathogen, making it the "most successful parasite." *T. gondii* infects virtually all nucleated cells in warm-blooded animals. The parasite forms a special membranous structure called a "parasitophorous vacuole (PV)." The host-parasite interaction takes place through the PV. In response to *T. gondii*, the host immune system produces inflammatory cytokines such as interleukins, chemokines, and interferons. Interferon- $\gamma$  (IFN- $\gamma$ ) is the most important host factor for inducing anti-*T. gondii* responses, which suppress and kill the parasites. One of the main projects in our laboratory is to identify the IFN- $\gamma$ -induced anti-*T. gondii* host defense mechanisms involved in innate and adaptive immunity. Recently, we found that IFN- $\gamma$ -inducible GTPases called GBPs are important for *T. gondii* PV disruption, and that their function in anti-*T. gondii* responses requires autophagy proteins; this suggests an unexpected link between IFN- $\gamma$ -induced immunity and autophagic pathways.

On the other hand, virulent *T. gondii* suppress IFN- $\gamma$ -induced host immunity and even manipulate host immune cells to maximize the virulence of the parasite. Another main project in our laboratory is to identify novel virulence mechanisms used by *T. gondii*. For example, we recently showed that a *T. gondii*-secreting virulence factor, GRA6, directly activates the host transcription factor NFAT4 to induce chemokines and recruit neutrophils to eradicate the parasite. Thus, our laboratory is focusing on host-parasite interactions via immunoparasitological mechanisms.



*Toxoplasma gondii*  
Pathogenic proteins are secreted from Dense granules and Rhoptry.



*Toxoplasma gondii* (green) proliferating inside macrophages (red).

### Staff

Asst. Prof. : Miwa Sasai / Asst. Prof. : MA JISU /  
Postdoc. : Hironori Bando / Grad. Student 4



Bacteria-gut interplay and the host immune response are the most critical issues in determining the fate of bacterial infections and the severity of the diseases. Our group has been studying the pathogenesis of mucosal infectious bacteria, such as *Helicobacter pylori*, *Shigella*, enteropathogenic *Escherichia coli*, and *Streptococcus pyogenes*, by defining the molecular and cellular mechanisms of infections and the roles of pathogenic factors as well as the host factors in infections.

## Staff

Asst. Prof. : Ryota Otsubo / Grad. Student 1

Associate Professor  
Hitomi Mimuro

## Profile

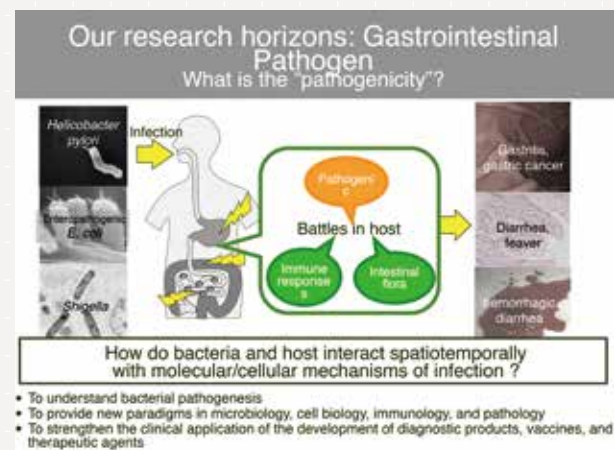
Dr. Mimuro received her Ph.D. from The University of Tokyo in 2004. She became Assistant professor at the Institute of Medical Science, The University of Tokyo in 2005 and worked for the same institution. She was appointed Associate Professor in RIMD in 2017 (also hold a post in The University of Tokyo).

## Publication

- (1) Epigenetic silencing of miR-210 increases the proliferation of gastric epithelium during chronic *Helicobacter pylori* infection. Kiga K., et al. *Nat Commun.* (2014) Sep 4;5:4497.
- (2) The immune receptor NOD1 and kinase RIP2 interact with bacterial peptidoglycan on early endosomes to promote autophagy and inflammatory signaling. Irving AT., et al. *Cell Host Microbe.* (2014) May 14;15(5):623-35.
- (3) *Shigella* IpaH7.8 E3 ubiquitin ligase targets glomulin and activates inflammasomes to demolish macrophages. Suzuki S., et al. *Proc Natl Acad Sci U S A.* (2014) Oct 7;111 (40):E4254-63.
- (4) BabA-mediated adherence is a potentiator of the *Helicobacter pylori* type IV secretion system activity. Ishijima N., et al. *J Biol Chem.* (2011) Jul 15;286.

In the Mimuro laboratory, researchers are exploring the pathogenesis of mucosal infectious bacteria, including *H. pylori*, *Shigella*, enteropathogenic *E. coli*, and *S. pyogenes*.

*H. pylori* transports effector proteins and other molecules into host epithelial cells via a Type IV secretion system and/or outer membrane vesicles. Researchers are studying how these effectors cause diseases such as gastritis, gastric ulcers, and cancer. They are also trying to elucidate the mechanisms that enable long-term infection of *H. pylori* in the stomach. In addition, researchers are focusing on the molecular mechanisms in the host that protect against infectious bacteria. The expected output of their research will not only shed further light on bacterial pathogenesis, but also provide a new paradigm in microbiology, cell biology, immunity, and pathology, and strengthen the molecular basis for developing diagnostic products, vaccines, animal models, and therapeutic agents.



## Clinical Training Course on Tropical Infectious Diseases in the Thailand

The age of global travel means that people can spread pathogens worldwide. Infectious diseases are now a global problem that extends beyond national borders. In Japan, there is a compelling need for experienced specialists to study these infectious diseases.

Since 2009, RIMD, together with the School of Medicine at Osaka University, has provided a clinical training course on Tropical Infectious Diseases in Thailand. The course provides medical doctors with clinical training on the diagnosis and treatment of infectious diseases and is supported by hospitals in Thailand. This training course provides a valuable opportunity for Japanese clinicians to gain clinical experience from hospital staff operating in a high-incidence area. Over 50 doctors participated in this training course, and the alumni are conducting basic/clinical research into infectious diseases or working for Medicines Sans Frontieres and various governmental organizations.



Hospitals participating in clinical training in Thailand.  
Doctors can learn directly from local staff.



Doctors gain hands-on experience during the training course.



## &lt;Hospitals for clinical training in Thailand&gt;

## Maesot:

Mae Sot General Hospital  
Mae La refugee camp  
Mae Tao Clinic  
Maeramad Hospital  
Shoklo Malaria Research Unit

## Udonthani:

Udon Thani Genelas Hospital

## Bangkok:

Ramathibodi Hospital, Mahidol University  
Queen Sirikit National Institute of Child Health

## Khon kaen:

Srinagarind Hospital, Khon Kaen University  
Khon Kaen General Hospital

<http://tmtc.biken.osaka-u.ac.jp/intention/index.html>





The immune system uses a wide range of receptors to protect against pathogens and facilitate their clearance. Innate immune receptors have lower diversity and specificity, and can elicit rapid responses, while there is a large repertoire of adaptive immune receptors that can bind to each ligand precisely and trigger more complex responses. Immune receptors can recognize both non-self and self ligands, and consequently induce different responses to protect the host. Our laboratory focuses on studying these receptors as well as their ligands and the mechanisms underlying the responses that they trigger.

### Professor Sho Yamasaki

#### Profile

Dr. Yamasaki received his Ph.D. from Kyoto University in 1999. After working at Mitsubishi Chemical Corporation and Chiba University Graduate School of Medicine, he worked for Research Center for Allergy and Immunology, RIKEN from 2004 to 2009. He was appointed as Professor in Medical Institute of Bioregulation, Kyushu University in 2009. He took his current position at RIMD from 2017.



#### Publication

- (1) C-type lectin receptor DCAR recognizes mycobacterial phosphatidyl-inositol mannosides to promote a Th1 response during infection. Toyonaga K., et al. *Immunity*. (2016) 45:1-13.
- (2) Dectin-2 is a direct receptor for mannose-capped lipoarabinomannan of mycobacteria. Yonekawa A., et al. *Immunity*. (2014) 41:402-13.
- (3) C-Type lectin MCL is an FcRγ-coupled receptor that mediates the adjuvanticity of mycobacterial cord factor. Miyake Y., et al. *Immunity*. (2013) 38:1050-62.
- (4) Direct recognition of the mycobacterial glycolipid, trehalose dimycolate, by C-type lectin Mincle. Ishikawa E., et al. *J. Exp. Med.* (2009)206:2879-88.
- (5) Mincle is an ITAM-coupled activating receptor that senses damaged cells. Yamasaki S., et al. *Nat. Immunol.* (2008)9:1179-88.
- (6) Mechanistic basis of pre-T cell receptor-mediated autonomous signaling critical for thymocyte development. Yamasaki S., et al. *Nat. Immunol.* (2006)7:67-75.

#### Staff

Asst. Prof. : Eri Ishikawa / Asst. Prof. : Chihiro Motozono /  
Postdoc. : Masahiro Nagata / Guest Researcher : Daiki Mori /  
Grad. Student 12

#### C-type lectin receptors (CLRs) sense both “non-self pathogens” and “damaged self”.

CLRs are involved in innate immunity; however, this family exhibits higher diversity and ligand specificity than other innate immune receptor families such as Toll-like receptors due to the wider variety of genes [Fig.1]. CLRs recognize pathogen-associated molecular patterns. We showed that Mincle (macrophage-inducible C-type lectin) recognizes the glycolipid TDM (trehalose-6,6'-dimycolate), a component of the *Mycobacterium tuberculosis* cell wall. This CLR acts as a sensor to trigger the immune response through a signaling pathway that involves FcRγ and CARD9, among other components. We also identified the ligands through which the CLRs MCL (macrophage C-type lectin), Dectin-2 (dendritic cell-associated C-type lectin-2), and DCAR (dendritic cell immunostimulating receptor) recognize *M. tuberculosis* and other pathogens, and elucidated some of the mechanisms by which they induce immune responses.

In addition, in a recent study, our group shed light on the function of Mincle in the recognition of endogenous ligands. Mincle can bind to β-glucosylceramide, a glycolipid that is released by host cells after damage. Thus, Mincle not only detects pathogens or foreign ligands, but also endogenous molecules released by damaged cells to activate the immune system and the response to “danger” situations.

We are presently investigating in further detail the recognition of both self and non-self ligands by this family of receptors and their role in immunity [Fig.2].

#### Self ligands are recognized by T cell receptors (TCRs) and play an important role in T cell persistence

T cells pass various selections of their TCRs before they are released from the thymus into the periphery. TCRs that weakly bind to self ligands cause T cell retention, and the signaling cascades induced by self ligands are important for T cell persistence but do not lead to T cell activation. Our objective is to clarify the recognition of “self” by TCRs and the distinct signals transduced by the same TCR upon stimulation with self and non-self ligands.

#### Novel T cell subsets contribute to autoimmune diseases

Recent evidence has shown that novel T cell subsets are responsible for autoimmune phenotypes that are comparable with human disorders. We are interested in the ligands that are recognized by these pathogenic T cells and the mechanisms via which the diseases develop. Based on the analysis of the corresponding subsets in human, we aim to design new methods to diagnose and treat autoimmune diseases.

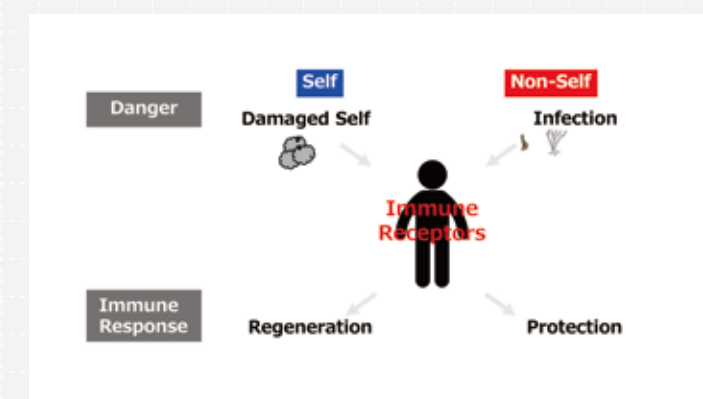


Fig.1 Immune Receptors are sensor for Dangers

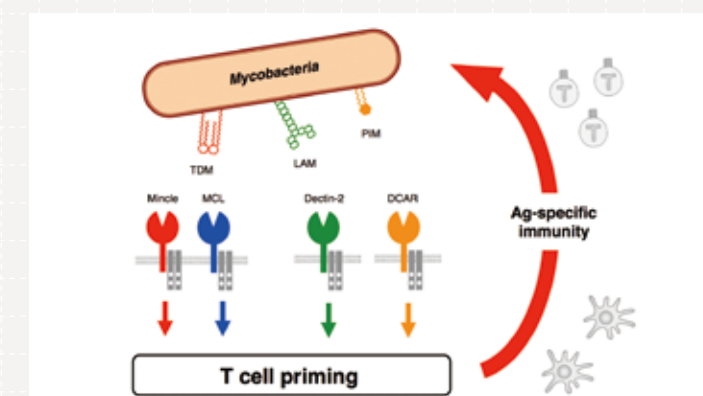


Fig.2 Cooperative function of CLRs against mycobacteria



Innate immunity is a defense system triggered by pattern recognition receptors, which recognize various pathogens such as bacteria, fungi, and viruses, and induce the production of inflammatory factors to trigger immune responses. To gain comprehensive understanding of the molecular mechanisms responsible for innate immunity *in vivo*, our lab focuses on the following themes:

### Professor Shizuo Akira (SUP)

#### Profile

Dr. Akira graduated Osaka University Medical School in 1977 and received his Ph.D. from the same institution in 1984. He spent the period from 1985 to 1987 as a Research Fellow in the Department of Microbiology and Immunology, California University. He returned to the Institute for Molecular and Cellular Biology in Osaka University where he remained until 1996. He was appointed his current position in 1999 after working in Hyogo College of Medicine for 3 years. He concurrently serve as the Director for WPI Immunology Frontier Research Center, Osaka University from 2007.



#### Publication

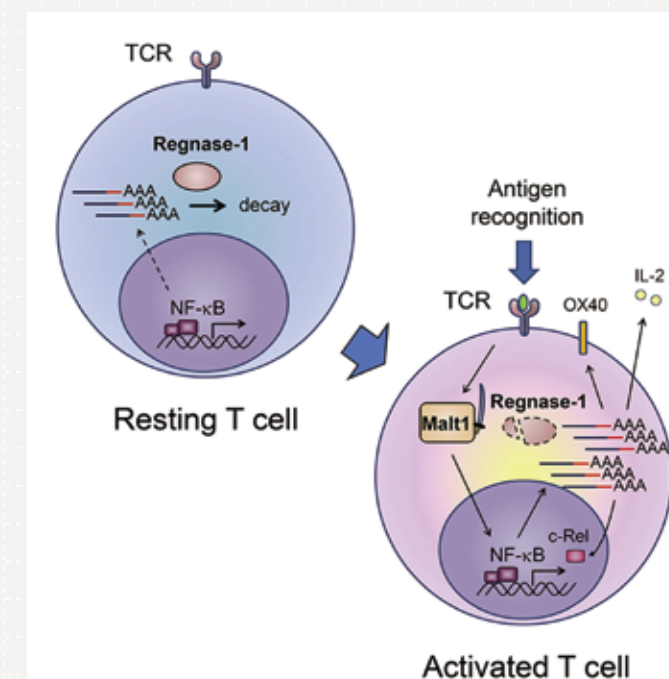
- (1) Identification of an atypical monocyte and committed progenitor involved in fibrosis. Satoh, T., et al. *Nature*. (2017) 541(7635):96-101.
- (2) Malt1-Induced Cleavage of Regnase-1 in CD4+ Helper T Cells Regulates Immune Activation. Uehata T., et al. *Cell*. (2013) 153(5):1036-1049.
- (3) Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. Satoh T., et al. *Nature*. (2013)495 (7442): 524-528.
- (4) The IκB kinase complex regulates the stability of cytokine-encoding mRNA induced by TLR-IL-1R by controlling degradation of regnase-1. Iwasaki H., et al. *Nat Immunol*. (2011) 12(12): 1167-1175.
- (5) The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. Satoh T., et al. *Nat Immunol*. (2010) 11 (10):936-944.
- (6) Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Matsushita K., et al. *Nature*. (2009) 458(7242):1185-1190.

### Exploration of the relationship between immune responses and mechanisms that ensure mRNA stability

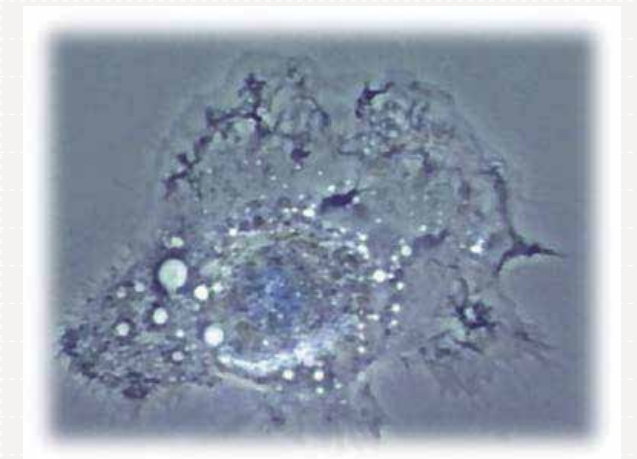
We have been investigating the comprehensive innate immune response induced by pattern recognition receptors that sense various pathogens. Recently, by studying the Toll-like receptor (TLR)-signaling pathway we found that a novel regulatory mechanism, "mRNA stability," controls inflammatory responses. Regnase-1, an endoribonuclease, constitutively degrades mRNAs encoding inflammatory cytokines. Once the TLR pathway is activated, the synthesis of mRNAs encoding inflammatory cytokines is promptly induced along with the degradation of Regnase-1 itself. As a result, mRNAs encoding inflammatory cytokines are stably expressed, resulting in an ongoing inflammatory response. Thus, endogenous Regnase-1 negatively regulates the stability of mRNAs encoding inflammatory cytokines in normal immune cells. Once pathogens invade cells, Regnase-1-mediated negative regulation is released, leading to inflammation. Moreover, TLR signals also suppress excessive inflammation by inducing synthesis of mRNA encoding Regnase-1. Currently, we are examining the molecular mechanism underlying the activity of Regnase-1 family member proteins and other related molecules to understand the relationship between mRNA stability and innate immune responses.

### Uncovering the novel functions of new macrophage subsets

Macrophages are leukocytes that eliminate invading bacteria by phagocytosis. There are two types of macrophage: M1 and M2. We identified a new type of M2 macrophage that is involved in various pathological disorders such as allergic response and metabolic syndromes. So far, we have identified a variety of "disease-specific macrophage subsets" that are independently associated with arteriosclerosis, autoimmune disease, cancer, and fibrosis. Currently, we are focusing on the role of these novel disease-specific macrophage subsets in different pathologies and are attempting to define these new macrophage subsets in detail.



Regnase-1 in CD4<sup>+</sup> T cells suppresses autoimmune disease in mice.



One subtype of disease-specific macrophage.

### Staff

Assoc. Prof. : Kazuhiko Maeda / Asst. Prof. : Takashi Satoh /  
SA Asst. Prof. : Hiroki Tanaka (SUP) / Postdoc. : Kanako Kuniyoshi /  
Undergrad. Student 4 / Grad. Student 11

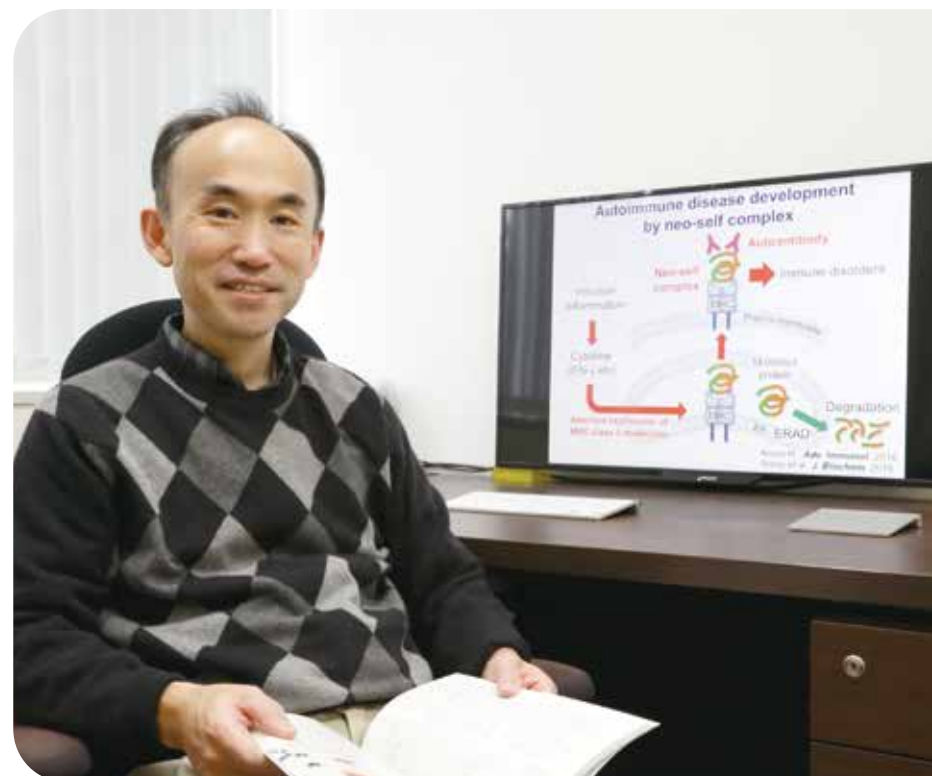


We have been studying interactions between pathogens and various paired receptors. In addition, we found that MHC class II molecules function as molecular chaperones to transport misfolded proteins to the cell surface. Analyses of misfolded proteins transported to the cell surface revealed that they are involved in autoimmune diseases by acting as a target for autoantibodies.

### Professor Hisashi Arase (SUP)

#### Profile

Prof. Arase received M.D. from Hokkaido University School of Medicine at 1990 and received Ph.D from Hokkaido University at 1994. Thereafter he worked as an assistant professor at Chiba University School of Medicine (1994), a research fellow at University of California San Francisco (2000), an associate professor at Chiba University (2002) and an associate professor at Research Institute for Microbial Diseases (2004). he is working as current position from 2006.



#### Publication

- (1) LILRA2 is an innate immune sensor for microbially cleaved immunoglobulins. Hirayasu K., et al. *Nature Microbiology*. (2016) 6:16054. doi: 10.1038/nmicrobiol.2016.54.
- (2) Rheumatoid Rescue of Misfolded Cellular Proteins by MHC Class II Molecules: A New Hypothesis for Autoimmune Diseases. Arase H. *Adv. Immunol.* (2015) 129:1-23.
- (3) Autoantibodies to IgG/HLA class II complexes are associated with rheumatoid arthritis susceptibility. Jin H., et al. *Proc. Natl. Acad. Sci. USA*. (2014) 111: 3787-92.
- (4) Neutrophil infiltration during inflammation is regulated by PILRa via modulation of integrin activation. Wang J., et al. *Nat. Immunol.* (2013) 14:34-40.
- (5) Myelin-associated glycoprotein mediates membrane fusion and entry of neurotropic herpesviruses. Suenaga T., et al. *Proc. Natl. Acad. Sci. USA* (2010) 107:866-71.
- (6) PILRa is a herpes simplex virus-1 entry co-receptor that associates with glycoprotein B. Satoh T., et al. *Cell* (2008) 132:935-44.

#### Staff

Assoc. Prof. : Tadahiro Suenaga / Asst. Prof. : Masako Kohyama /  
Postdoc. : Fumiji Saito / Postdoc. : Kazuki Kishida /  
Postdoc. : Wataru Nakai / Undergrad. Student 3 / Grad. Student 9

### Interaction between immune receptors and pathogens

Immune cells express “paired” activating and inhibitory receptors that are highly homologous. The inhibitory receptors recognize self-antigens and downregulate immune response to the self. On the other hand, we found that some inhibitory receptors are used by pathogens for immune evasion (Fig. 1). By contrast, we found that LILRA2, an orphan activating receptor expressed on human myeloid cells, recognizes abnormal immunoglobulins cleaved by microbial proteases but not normal immunoglobulins. Because immunoglobulins are important for host defense, their degradation is very dangerous in terms of immunity (Fig. 2). In this way, paired receptors play an important role not only in immune regulation but also in host defense against pathogens.

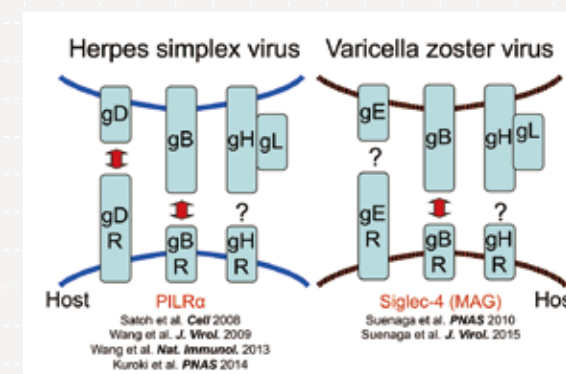
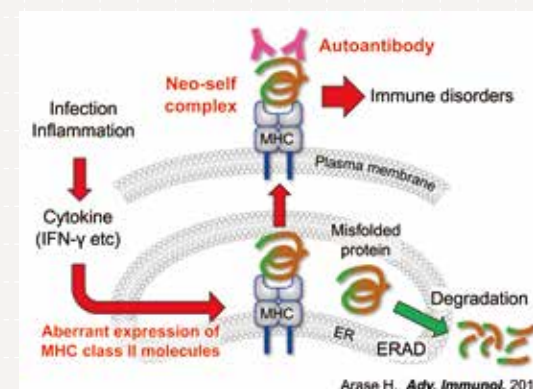


Fig. 1. Immune evasion of herpesviruses via paired inhibitory receptors.

Inhibitory receptors play an important role in immune regulation, whereas pathogens exploit inhibitory receptors for immune evasion. Especially, we have found that inhibitory receptors are used by herpesviruses to enter into host cells.



### Misfolded proteins complexed with MHC class II molecules trigger autoimmune disease

Allelic polymorphisms in MHC class II molecules are strongly associated with susceptibility to many autoimmune diseases. However, it is unclear how MHC class II molecules are involved in autoimmune disease susceptibility. We found that misfolded cellular autoantigens are rescued from protein degradation by MHC class II molecules. Furthermore, we found that misfolded proteins complex with MHC class II molecules and become targets for autoantibodies. Autoantibody binding to misfolded proteins that are transported to the cell surface by MHC class II molecules correlated strongly with susceptibility to autoimmune disease, suggesting that misfolded proteins, which normally would not be presented to the immune system, can be targets for autoantibodies by acting as “neo self” antigens, which are involved in the pathogenicity of autoimmune diseases (Fig.3).

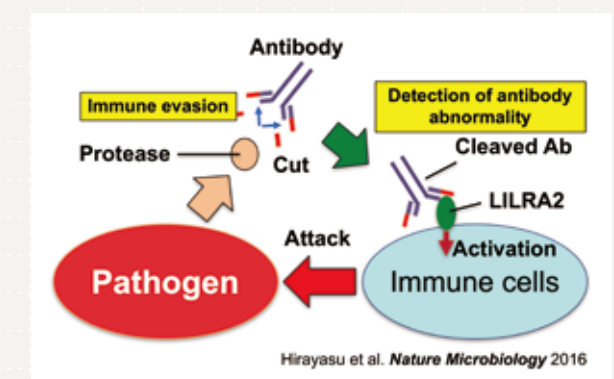


Fig. 2. Activating paired receptors play a role in host defense against bacterial infection

Activating paired receptor, LILRA2, recognizes immunoglobulin cleaved by bacterial protease activate innate immune cells (Hirayasu et al. *Nat. Microbiol.* 2016).

Fig. 3. Misfolded proteins complexed with MHC class II molecules are targets for autoantibodies.

Misfolded cellular proteins are transported to the cell surface without being processed to peptides by associating with MHC class II molecules in the ER. Furthermore, misfolded proteins complexed with MHC class II molecules encoded by disease-susceptible alleles are specifically recognized by autoantibodies. This suggests that misfolded proteins complexed with MHC class II molecules are natural autoantigens for autoantibodies, which affect susceptibility to autoimmune diseases (Arase *Adv. Immunol.* 2016).



It has become apparent that aging has a major impact on the incidence of cancers. However, the underlying mechanisms are unclear. We think that cellular senescence plays a key role. In our laboratory, we are aiming to understand the roles and mechanisms of cellular senescence *in vivo*. We believe that understanding the molecular mechanisms underlying cellular senescence *in vivo* will provide valuable insight into the development of aging-associated diseases such as cancer, and open up new possibilities for their control.

## Professor Eiji Hara

### Profile

Dr. Hara received his Ph.D. from Tokyo University of Science in 1993. After working at Imperial Cancer Research Fund Laboratories, U.K. (Post-doctoral Fellow), Cancer Research UK-Paterson Institute, U.K. (Group Leader) and the Institute for Genome Research, University of Tokushima (Professor), he was appointed Division Chief in the Cancer Institute, Japanese Foundation for Cancer Research in 2008. He took his current position at RIMD from 2015.



### Publication

- (1) Ablation of the  $p16^{INK4a}$  tumour suppressor reverses ageing phenotypes of *klotho* mice. Sato S., et al. *Nature Communications* (2015) 6:7035.
- (2) Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Yoshimoto S., et al. *Nature* (2013) 499:97-101.
- (3) DNA damage signaling triggers degradation of histone methyltransferases through APC/C<sup>cdh1</sup> in senescent cells. Takahashi A., et al. *Molecular Cell* (2012) 45:123-31.
- (4) Real-time *in vivo* imaging of  $p16^{INK4a}$  reveals cross-talk with p53. Yamakoshi K., et al. *Journal of Cell Biology* (2009) 186:393-407.
- (5) Mitogenic signalling and the  $p16^{INK4a}$ -Rb pathway cooperate to enforce irreversible cellular senescence. Takahashi A., et al. *Nature Cell Biology* (2006) 8:1291-7.
- (6) Opposing effects of Ets and Id proteins on  $p16^{INK4a}$  expression during cellular senescence. Ohtani N., et al. *Nature* (2001) 409:1067-70.

## Staff

Assoc. Prof. : Sugiko Watanabe / Asst. Prof. : Shimpei Kawamoto /  
SA Asst. Prof. : Atsushi Okuma / Postdoc. : Masahiro Wakita /  
Grad. Student 4

## Exploring the physiological roles and mechanisms underlying cellular senescence *in vivo*

Cellular senescence is the state of irreversible cell cycle arrest that can be induced by a variety of potentially oncogenic stimuli and has, therefore, long been considered to suppress tumorigenesis. We reported that  $p16^{INK4a}$  and  $p21^{Waf1/Cip1}$ , both cyclin-dependent kinase inhibitors, play crucial roles in both the onset and establishment of cellular senescence in cell culture and in mouse models. Recently, we generated transgenic mice expressing firefly luciferase under the control of the  $p16^{INK4a}$  or  $p21^{Waf1/Cip1}$  gene promoters. Using these senescence response reporter mice in combination with knockout mice, we are investigating the timing and, hence, the likely roles and mechanisms, of cellular senescence *in vivo*.

## Understanding the molecular mechanisms underlying inflammatory diseases induced by senescence-associated secretory phenotypes (SASPs)

In addition to stable cell cycle arrest, senescent cells also develop senescence-associated secretory phenotypes (SASPs), which contribute both positively and negatively to the onset of inflammatory diseases such as cancer (depending on the biological context). Despite considerable progress in understanding the biological roles of SASPs, far less is known about how they are induced.

Thus, a greater understanding of the underlying molecular mechanisms will lead to novel therapeutic strategies for various aging-associated diseases, including cancer.

Similar to aging, obesity is associated with cancer. However, the underlying mechanisms are not well understood. Recently, we traced the association between obesity and increased cancer risk to gut microbiota communities that produce DNA-damaging bile acid. We found that DNA-damaging bile acid promotes development of obesity-associated liver cancer by inducing SASPs in hepatic stellate cells. We are now focusing on the potential clinical implications of these findings.

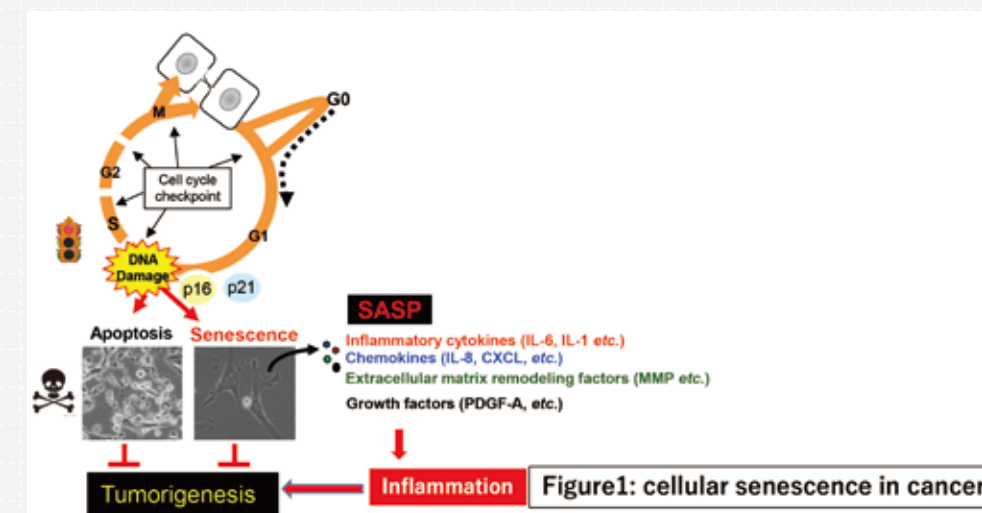


Fig. 1. Cellular senescence initially inhibits proliferation of damaged cells, thereby acting as a fail-safe mechanism. However, in the long term, senescent cells may eventually promote tumorigenesis via SASPs.

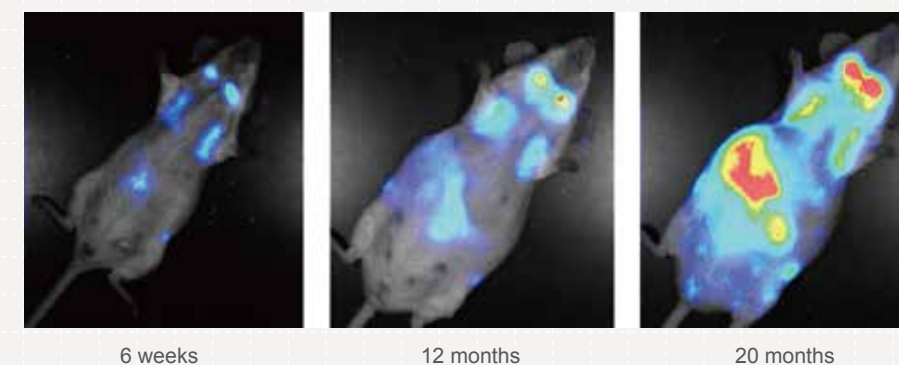


Fig. 2. Real-time bioluminescence imaging of  $p16^{INK4a}$  gene expression during aging (*Journal of Cell Biology* 186: 393-407. 2009).

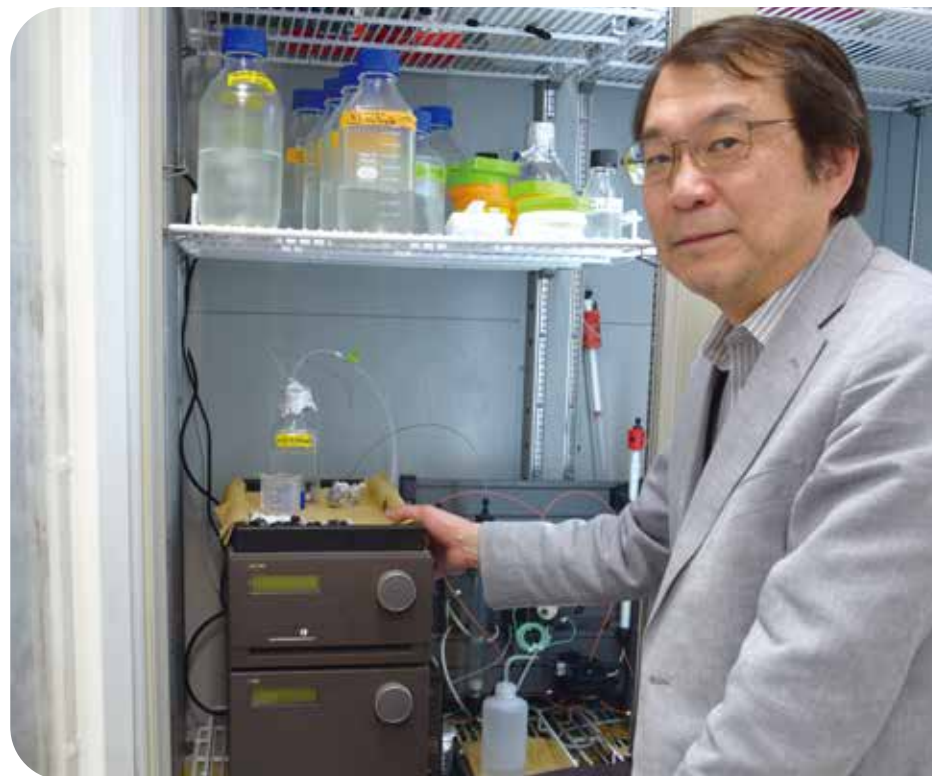


Cancer develops due to accumulation of mutations within a cell, which can then become malignant through immortalization and transformation. The malignant traits of cancer cells occur as they evade cancer inhibitory mechanisms such as apoptosis and senescence and acquire capacity for autonomous proliferation. In addition, cancer cells acquire invasive and metastatic characteristics through the loss of intercellular communication and altered cell morphology.

## Professor Masato Okada

### Profile

Dr. Okada graduated Kyoto University School of Science in 1981 and received his Ph.D. from Osaka University in 1988. He worked as a Research Associate at the Institute for Protein Research in Osaka University and became an Associate professor in 1996 in the same institution. He was appointed current position as a Professor of RIMD in 2000.



### Publication

- (1) Polarization of M2 macrophages requires Lamtor1 that integrates cytokine and amino-acid signals. Kimura T., et al. *Nat Commun.* (2016) 7:13130, doi: 10.1038/ncomms13130.
- (2) The Rho guanine nucleotide exchange factor ARHGEF5 promotes tumor malignancy via epithelial-mesenchymal transition. Komiya Y., et al. *Oncogenesis* (2016) 5: e258
- (3) p18/LAMTOR1: a late endosome/lysosome-specific anchor protein for the mTORC1/MAPK signaling pathway. Nada S., et al. *Methods Enzymol* (2014) 535:249-63
- (4) The novel lipid raft adaptor p18 controls endosome dynamics by anchoring the MEK-ERK pathway to late endosomes. Nada S., et al. *EMBO J.* (2009) 28:477-89
- (5) The lipid raft-anchored adaptor protein cbp controls the oncogenic potential of c-Src. Oneyama C., et al. *Mol Cell* (2008) 30:426-36
- (6) Transmembrane phosphoprotein Cbp regulates the activities of Src-family tyrosine kinases. Kawabuchi M., et al. *Nature* (2000) 404:999-1003

## Staff

Assoc. Prof. : Shigeyuki Nada / Assoc. Prof. : Norikazu Yabuta /  
Asst. Prof. : Kentaro Kajiwara / Postdoc. : Akira Ogawa /  
Undergrad. Student 3 / Grad. Student 10

## Src and cancer development

Src is a signaling molecule that localizes to the sub-membrane and was the first oncogene to be discovered. Normal tissues retain morphology by maintaining contact between neighboring cells via cell-cell junctions; however, cancer cells exhibit altered morphology (shown in Fig. 1) and undergo invasion and metastasis by secreting growth factors and proteases. Our laboratory has examined the role of Src as an activator of signaling pathways that control remodeling of the cytoskeleton, which contributes to motility by inducing morphological changes. In addition, Src is involved in cell membrane-mediated signaling pathways that promote expression of genes encoding proteases, thereby leading to malignancy. We aim to further elucidate the detailed molecular mechanisms by which Src affects cancer cell invasion and metastasis.

Interestingly, unlike other oncogenes, Src harbors no mutations. We found that Src is involved in a phenomenon called "cell competition," in which cells interact and compete with each other, producing a "winner" based on their relative fitness. We anticipate that revealing the relationship between Src and cell competition will increase our understanding of the function of Src in cancer development; these studies are ongoing.

## The molecular mechanism underlying p18/Ragulator and mTOR nutrient signaling

mTOR is responsible for nutrition- and growth-related signaling in cells, and is involved in various biological phenomena. Our laboratory discovered that the p18 protein acts as an adaptor for molecules involved in regulating mTOR, and that it plays a crucial role in activating mTOR. We will continue our research into the molecular mechanism by which p18 regulates mTOR using protein structural analysis and by studying the molecular interactions between other factors involved in mTOR regulation.

In addition, we are studying the molecular mechanisms underlying cancer defense in naked mole rats (NMR). NMR are rodents that are similar to mice; however, they are unique in that they have an exceptionally long life span (up to 10 times that of mice). They also exhibit significant resistance to aging and cancer. Our laboratory focuses on identifying the molecular mechanisms that allow NMR to acquire these traits.

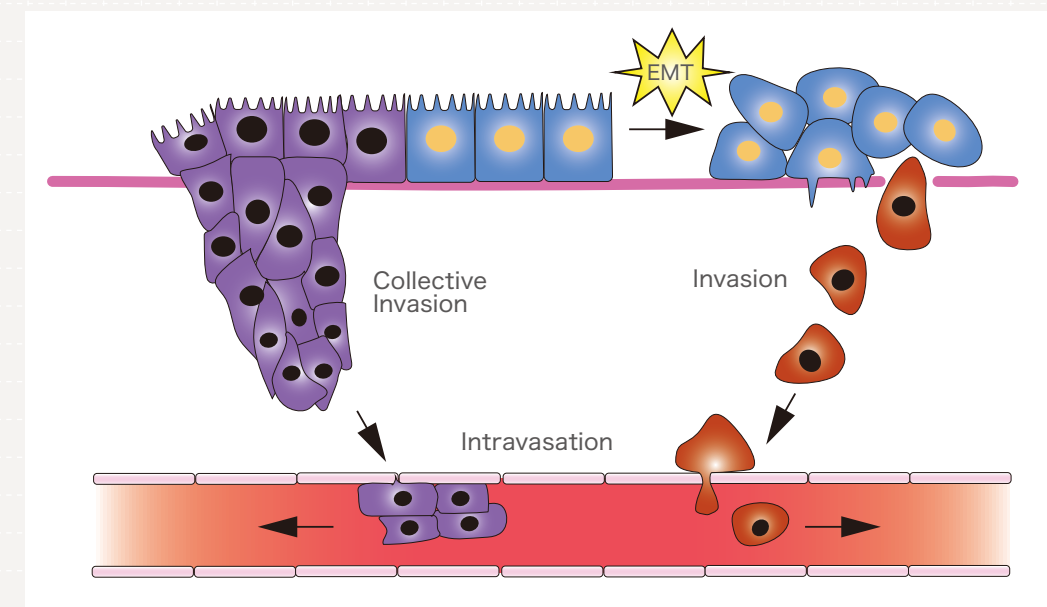


Fig. 1. Invasion and metastasis of cancer cells

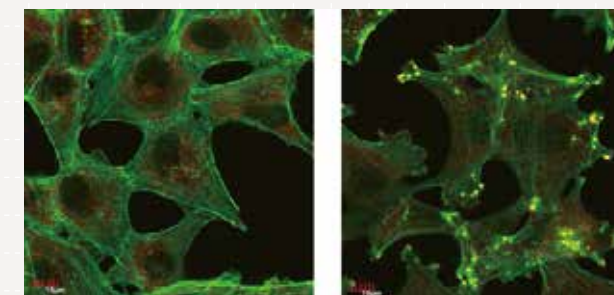


Fig. 2. Src activation induces morphological changes and increases cell mobility.

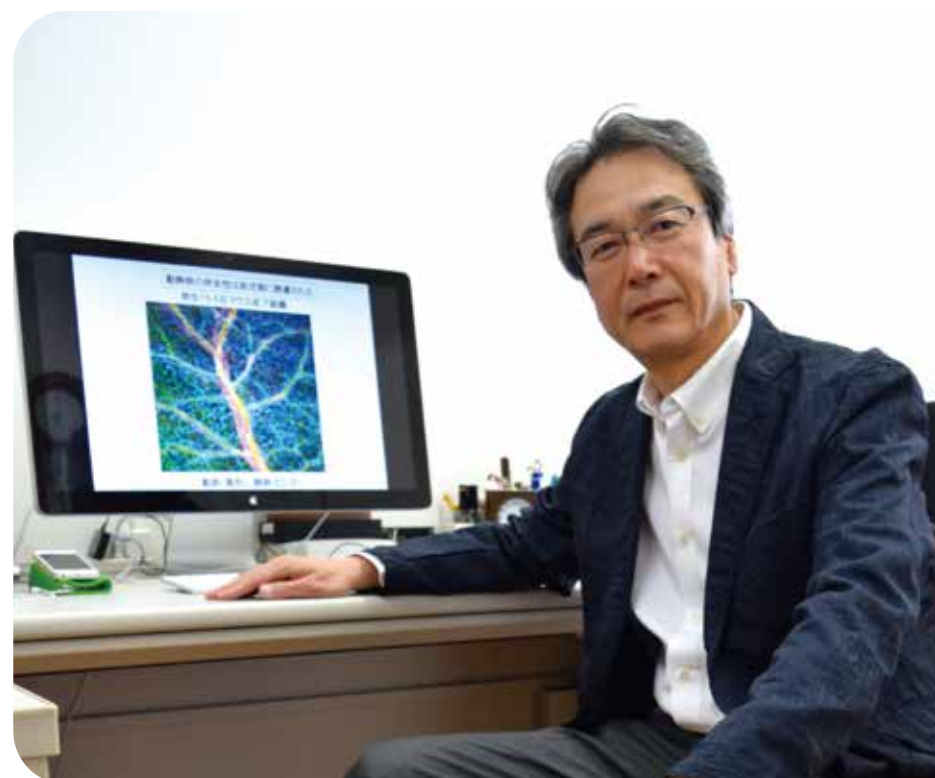


Tissue-specific stem cells continuously produce terminally differentiated functional cells and maintain organ integrity. Blood vessels supply oxygen and nutrients to all tissues; tissues and organs cannot develop without blood vessel formation. Our aim is to elucidate the cellular and molecular mechanisms underlying vascular formation (particularly those involving stem cells) and to develop strategies to manage patients with vascular diseases.

## Professor Nobuyuki Takakura

### Profile

Dr. Takakura obtained his Ph.D in Graduate School of Medicine, Kyoto University in 1997. He was appointed Professor of RIMD in 2006 after working at Kumamoto University as an assistant professor for 4 years and Kanazawa University as a professor for 5 years.



### Publication

- (1) Endothelial side population cells contribute to tumor angiogenesis and antiangiogenic drug resistance. Naito H., et al. *Cancer Research* (2016) 76 (11):3200-10.
- (2) APJ Regulates Parallel Juxtapositional Alignment of Arteries and Veins in the skin. Kidoya H., et al. *Dev Cell* (2015) 33 (3):247-59.
- (3) Identification and characterization of a resident vascular stem/progenitor cell population in preexisting blood vessels. Naito H., et al. *EMBO J* (2012) 31(4): 842-55.
- (4) Spatial and temporal role of the apelin/APJ system in the caliber size regulation of blood vessels during angiogenesis. Kidoya H., et al. *EMBO J* (2008) 27(3):522-34.
- (5) A role for hematopoietic stem cells in promoting angiogenesis. Takakura N., et al. *Cell* (2000) 102(2):199-209.
- (6) Critical role of the TIE2 endothelial cell receptor in the development of definitive hematopoiesis. Takakura N., et al. *Immunity* (1998) 9(5):677-86.

### Staff

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Postdoc. : Jia Wei Zhen / Postdoc. : Fumitaka Muramatsu

### Mechanism of vascular formation

Tissue homeostasis in all organs is maintained via a highly hierarchal architecture of blood vessels, which is precisely regulated in an organ-specific manner. We are examining how blood vessel diversity is regulated, focusing on the processes of angiogenesis and blood vessel maturation. Our recent studies clarified that arterial-venous alignment is regulated by the apelin/APJ system and is critical for thermoregulation (Kidoya, *Dev Cell* 2015).

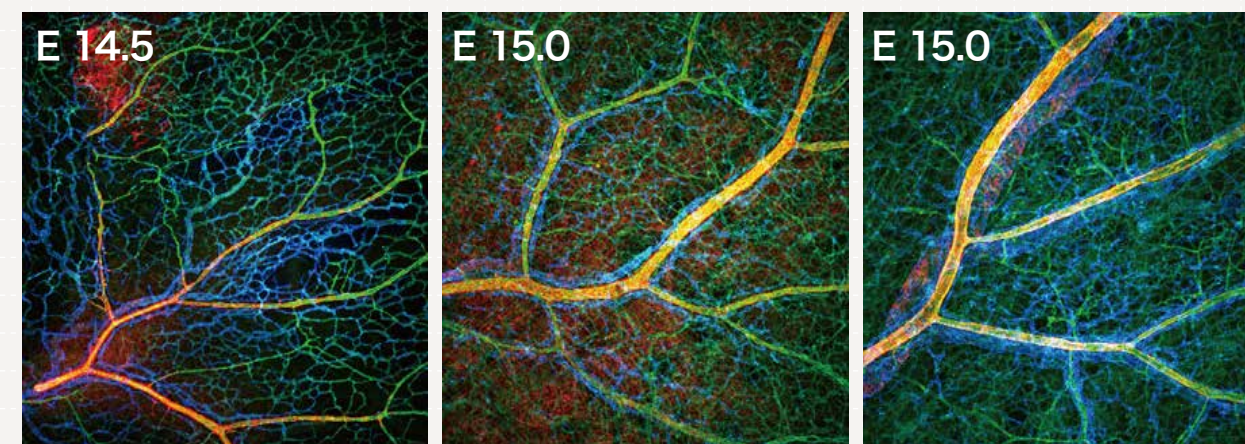
### Stemness and vascular niche

Stem cells localize in perivascular areas in many organs. Cells that comprise such a vascular niche regulate the "stemness" of stem cells. In our cancer stem cell (CSC) model based on PSF1 promoter activity, we found that CSCs proliferate and survive in the vascular niche (Nagahama, *Cancer Res* 2010, Kinugasa, *Stem Cells* 2014). Regulation of the vascular niche is a promising approach to inhibiting tumor growth. Because blood vessels developing

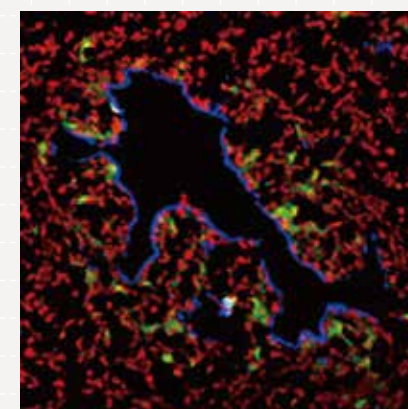
in the tumor microenvironment are immature and abnormal, normalization of blood vessel development must control CSCs in the vascular niche. Vascular normalization also improves anti-tumor immunity and drug delivery. Therefore, we are seeking ways to normalize blood vessels within tumors.

### Development of tissue regeneration methods based on endothelial stem cells

We have identified endothelial stem cells in pre-existing blood vessels and showed their utility for vascular regeneration (Naito, *EMBO J* 2012). Recently, we found that such endothelial stem cells affect the resistance of cancer cells to anti-angiogenic therapy (Naito, *Cancer Res* 2016). We are examining how endothelial stem cells develop and how they are maintained during development with a view to using this cell population to treat vascular disease.



**Fig. 1.** Vascular development in mouse embryos. Hierarchal architecture of blood vessels accompanied by arterial (yellow)–venous (blue) alignment. Green; endothelial cells.



**Fig. 2.** Endothelial cells (blue) and CSCs (green) in a tumor. CSCs localize at the perivascular area, the so called "vascular niche."



Most cancers originate from epithelial cells. Normal epithelial cells form a sheet-like tissue structure in which cells are tightly attached to each other and to the basement membrane. Through malignant progression, cells proliferate and expand by invading surrounding tissues. Furthermore, cells metastasize to distant organs via blood vessels, forming often incurable tumors. Our aim is to elucidate the mechanism underlying this mysterious process of cancer development.

## Professor Hiroaki Miki

### Profile

Dr. Miki received his Ph.D from University of Tokyo in 1998. He was appointed Professor in RIMD after working at the Institute of Medical Science, University of Tokyo and at the Institute for Protein Research, Osaka University.



### Publication

- (1) Phosphocysteine in the PRL-CNNM pathway mediates magnesium homeostasis. Gulerez et al. *EMBO Rep.* (2016) 17(12):1890-1900.
- (2)  $Mg^{2+}$  Extrusion from Intestinal Epithelia by CNNM Proteins Is Essential for Gonadogenesis via AMPK-TORC1 Signaling in *Caenorhabditis elegans*. Ishii T., et al. *PLoS Genet.* (2016) 12(8):e1006276.
- (3) Membrane protein CNNM4-dependent  $Mg^{2+}$  efflux suppresses tumor progression. Funato Y., et al. *J Clin Invest.* (2014) 124(12):5398-5410.
- (4) Basolateral  $Mg^{2+}$  extrusion via CNNM4 mediates transcellular  $Mg^{2+}$  transport across epithelia: a mouse model. Yamazaki D., et al. *PLoS Genet.* (2013) 9(12):e1003983.
- (5) Thioredoxin mediates oxidation-dependent phosphorylation of CRMP2 and growth cone collapse. Morinaka A., et al. *Sci Signal.* (2011) 4(170):ra26.
- (6) Nucleoredoxin sustains Wnt/ $\beta$ -catenin signaling by retaining a pool of inactive dishevelled protein. Funato Y., et al. *Curr Biol.* (2010) 20(21):1945-52.

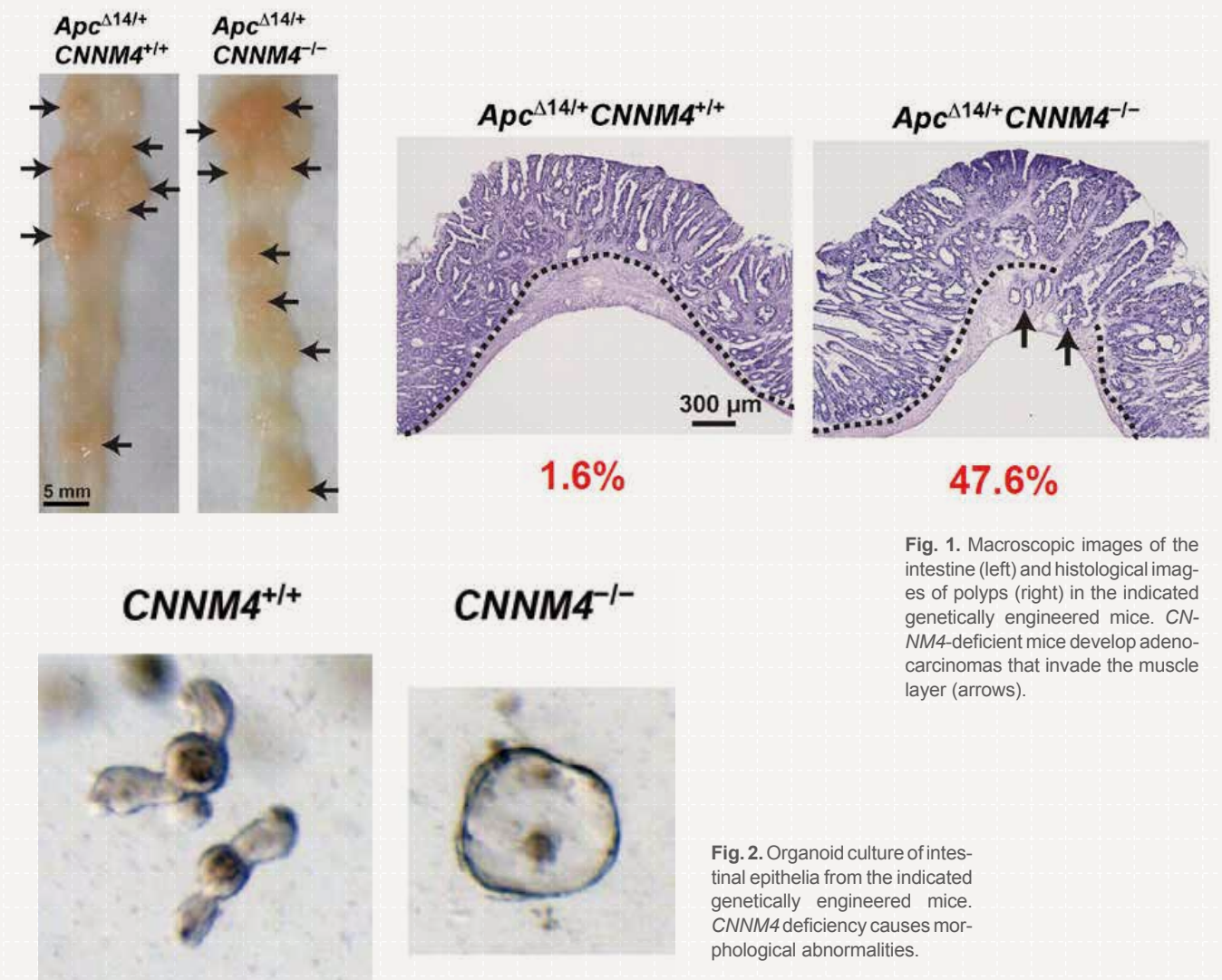
## Staff

Asst. Prof. : Daisuke Yamazaki / Asst. Prof. : Yosuke Funato /  
Postdoc. : Osamu Hashizume / Grad. Student 6

## Role of PRL in malignant progression of cancers

PRL is highly expressed in malignant tumors and promotes cancer metastasis. We discovered that PRL associates with CNNM4, a  $Mg^{2+}$  transporter, and inhibits its  $Mg^{2+}$  transporting activity. Moreover, we also found that intestinal polyps became malignant and invaded the surrounding muscle tissue when *CNNM4* was disrupted. At present, we are investigating the functional relationship between cancer malignancy and  $Mg^{2+}$  dyshomeostasis caused by CNNM4 inhibition.

In normal epithelial tissues, cells are attached to each other and collectively maintain their structure; these characteristics are disrupted in cancer tissues. Forced expression of PRL in epithelial cells cultured on matrix gels induced a marked change in their morphology; some cells invaded into the matrix only when PRL-expressing cells were surrounded by non-expressing cells. These results suggest that physical interaction between PRL-expressing cells and non-expressing cells stimulates invasive behavior during malignant progression. We are trying to clarify the molecular mechanism underlying this function of PRL.



**Fig. 1.** Macroscopic images of the intestine (left) and histological images of polyps (right) in the indicated genetically engineered mice. *CNNM4*-deficient mice develop adenocarcinomas that invaded the muscle layer (arrows).

## Functional analyses based on organoid culture of intestinal epithelia

A method of culturing intestinal epithelia in 3D matrix gels that mimic *in vivo* situations was recently developed; the system is called organoid culture. In this system, intestinal epithelial cells differentiate and form a structure comprising a monolayer sheet of cells. We are using this organoid culture system to investigate the role of PRL/CNNM in cell proliferation, differentiation, and cancerous transformation.

Many oncogenes and anti-oncogenes involved in regulating cell proliferation and survival have been identified. By contrast, characteristics involved in transformation of epithelial cells in a 3D space, which accompany architectural changes (such as invasion and metastasis) in tissues, remain unclear. For example, how do cancer cells exit the epithelial tissue in which they are "born" and expand their territory by invading surrounding tissues? We are tackling these problems and trying to identify the mechanisms underlying cancer development.



In the past, animals harboring natural mutations have been used to elucidate the mechanisms underlying various diseases. In the “post-genome project era,” genetically modified animals play a key role in basic molecular biological investigations and act as models of human disease. Our laboratory studies the mechanisms underlying mammalian reproductive systems through genetic manipulation of animal models.

## Professor Masahito Ikawa (SUP)

### Profile

Dr. Ikawa received his Ph.D. from Osaka University in 1997. After working as JSPS postdoctoral fellow and a Research Associate at Genome Information Research Center in Osaka University, he spent 2 years at The Salk Institute in the USA as a Research Associate. After returning to Osaka University in 2002, he became an Associate Professor in 2004 and was appointed to the current position in 2012. He was awarded JSPS Prize in 2013. His lifework is to study mammalian reproductive systems using genetically engineered mice.



### Publication

- (1) Viable offspring after imaging of  $Ca^{2+}$  oscillations and visualization of the cortical reaction in mouse eggs. Stout Y. et al., *Biol Reprod.* (2017) Mar 1;96 (3):563-575.
- (2) CRISPR/Cas9 mediated genome editing in ES cells and its application for chimeric analysis in mice. Oji A., et al. *Sci Rep.* (2016) 6:31666.
- (3) Structural and functional insights into IZUMO1 recognition by JUNO in mammalian fertilization. Kato K., et al. *Nat Commun.* (2016) 7:12198.
- (4) Genome engineering uncovers 54 evolutionarily conserved and testis-enriched genes that are not required for male fertility in mice. Miyata H., et al. *Proc Natl Acad Sci USA.* (2016) 113(28):7704-10.
- (5) Generation of Hprt-disrupted rat through mouse-rat ES chimeras. Isotani A., et al. *Sci Rep.* (2016) 6:24215.
- (6) Sperm calcineurin inhibition prevents mouse fertility with implications for male contraceptive. Miyata H., et al. *Science.* (2015) 350(6259):442-5.

### Staff

Assoc. Prof.: Yuhkoh Satouh (SUP) / Asst. Prof.: Yoshitaka Fujihara /  
Asst. Prof.: Haruhiko Miyata / Asst. Prof.: Taichi Noda / SA Asst. Prof.: Daiji Kiyozumi (SUP) /  
Postdoc.: Keisuke Shimada / Postdoc.: Castaneda Julio Manuel / Postdoc.: Kaori Nozawa /  
Postdoc.: Nobuyuki Sakurai / Guest Professor: Martin M. Matzuk /  
Guest Researcher: Masaru Okabe / Undergrad. Student 4 / Grad. Student 7

### Analysis of molecular mechanisms involved in mammalian gametogenesis, fertilization, and implantation

We were the first laboratory in the world to produce genetically modified mice that express green fluorescent protein (GFP) throughout the body (Fig. 1). These green fluorescent mice are useful for many types of research project. Indeed, we used these animals to label sperm with fluorescent protein and visualize the fertilization process (*Exp Anim.* 2010; *JCS.* 2010, 2012; *PNAS.* 2012, 2013) (Fig. 2).

Recently, we found that calcineurin (PPP3CC/PPP3R2) is essential for sperm motility and male fertility (*Science.* 2015). Inhibiting sperm calcineurin may lead to the development of a reversible male contraceptive.

### Development of new technologies for producing genetically modified animals

Another tool improved by work in our laboratory is lentiviral (LV) vector-mediated genetic manipulation *in vivo*. We devel-

oped the technique of placenta-specific gene manipulation by transducing blastocyst stage embryos with LV vectors (*Nat Biotechnol.* 2007; *PNAS.* 2011). Using this technique, we are trying to elucidate the mechanism underlying implantation and placentation.

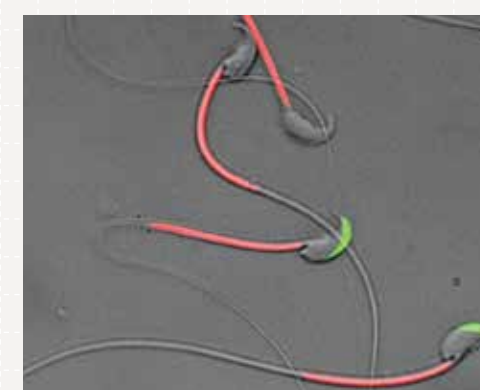
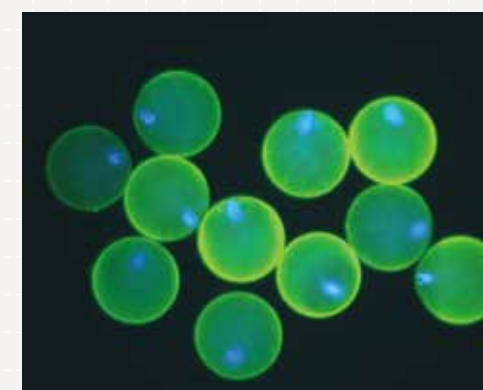
We also established rat embryonic stem (ES) cells and generated mouse-rat chimeric animals. We would like to use this animal model to study body/organ size control *in vivo*; indeed, this method may enable derivation of various organs from ES or iPS cells (*Genes Cell.* 2011; *Sci Rep.* 2016).

Our recent interest is using the CRISPR/Cas9 system to generate genetically modified animals to study fertilization, implantation, and placentation. We have had success in mice and rats using sgRNA/Cas9-expressing plasmids (*Sci Rep.* 2013,2016; *DGD.* 2014; *PNAS.*2016; *Nat. Commun.* 2016).

Our laboratory and the Animal Resource Center for Infectious Diseases (<http://www.arcid.biken.osaka-u.ac.jp/>) offer support services such as generation of genetically modified animals, *in vitro* fertilization, and cryopreservation of mouse strains. For more information, please visit our homepage (<http://www.egr.biken.osaka-u.ac.jp/index.php>).



**Fig. 1.** GFP-expressing mice are useful for many types of research project. Genetically modified animals play a key role in basic molecular biology-based investigations and are good models for studying human disease.



**Fig. 2.** Mouse eggs (left) and sperm (right) labeled with fluorescent proteins. These gametes are used to visualize the fertilization process. (Figs from *Exp. Anim.* 59(1), 105-7, 2010)



We are a bioinformatics laboratory, which means that we use computational methods to study problems that are difficult or impossible to investigate experimentally. Some of the problems we work on include: analysis of B and T cell receptor repertoires, protein-nucleotide interactions and multiple sequence alignment of protein and nucleotide sequences. These themes are described in more detail below.

 Professor  
**Daron M. Standley**

## Profile

Prof. Standley received his PhD in Chemistry from Columbia University in 1998. He then joined Schrodinger, Inc. where he worked as a scientific software developer for five years. In 2003 he moved to the Institute for Protein Research, Osaka University as a Senior Scientist. He joined the Immunology Frontier Research Institute (IFReC) as a Principal Investigator in 2008 and, after a two-year cross-appointment at Kyoto University's Institute for Virus Research, became a Professor full time at the Research Institute for Microbial Diseases in 2016.

## Profile

Prof. Standley received his PhD in Chemistry from Columbia University in 1998. He then joined Schrodinger, Inc. where he worked as a scientific software developer for five years. In 2003 he moved to the Institute for Protein Research, Osaka University as a Senior Scientist. He joined the Immunology Frontier Research Institute (IFReC) as a Principal Investigator in 2008 and, after a two-year cross-appointment at Kyoto University's Institute for Virus Research, became a Professor full time at the Research Institute for Microbial Diseases in 2016.



## Publication

- (1) Kotai Antibody Builder: automated high-resolution structural modeling of antibodies. Yamashita, K. et al. **Bioinformatics** 30, 3279-3280 (2014).
- (2) Quantifying sequence and structural features of protein-RNA interactions. Li, S., Yamashita, K., Amada, K. M. & Standley, D. M. **Nucleic Acids Res** 42, 10086-10098 (2014).
- (3) Malt1-induced cleavage of regnase-1 in CD4(+) helper T cells regulates immune activation. Uehata, T. et al. **Cell** 153, 1036-1049 (2013).
- (4) MAFFT multiple sequence alignment software version 7: improvements in performance and usability. Katoh, K. & Standley, D. M. **Mol Biol Evol** 30, 772-780 (2013).
- (5) SeSAW: balancing sequence and structural information in protein functional mapping. Standley, D. M., Yamashita, R., Kinjo, A. R., Toh, H. & Nakamura, H. **Bioinformatics** 26, 1258-1259 (2010).
- (6) Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Matsushita, K. et al. **Nature** 458, 1185-1190 (2009).

- ## Publication
- (1) Kotai Antibody Builder: automated high-resolution structural modeling of antibodies. Yamashita, K. et al. **Bioinformatics** 30, 3279-3280 (2014).
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  - (3) Malt1-induced cleavage of regnase-1 in CD4(+) helper T cells regulates immune activation. Uehata, T. et al. **Cell** 153, 1036-1049 (2013).
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  - (6) Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Matsushita, K. et al. **Nature** 458, 1185-1190 (2009).

**Staff**

Assoc. Prof. : Kazutaka Katoh / Asst. Prof. : Songling Li /  
Researcher. : John Rozewicki

**Staff**

Assoc. Prof. : Kazutaka Katoh / Asst. Prof. : Songling Li /  
Researcher. : John Rozewicki

## B and T cell receptor repertoires

## B and T cell receptor repertoires

A healthy immune system maintains a vast repertoire of B and T cells that can recognize a wide range of molecules. Functional analysis of B and T cell receptor sequences has the potential to reveal not only biomarkers for disease but also therapeutic compounds. Indeed, immune-based therapies, primarily based on engineered B cell receptors, are now the fastest-growing area in pharma. We are developing bioinformatics methods to mine immune receptor sequence data in order to accelerate discovery of novel therapeutic compounds.

## Protein-nucleotide interactions

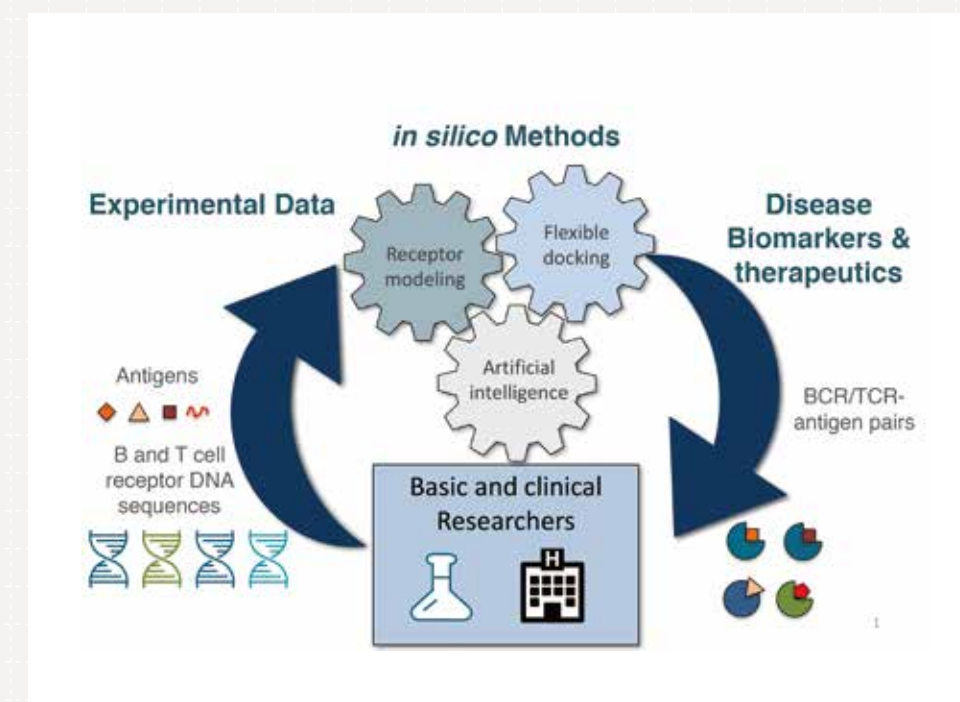
## Protein-nucleotide interactions

Protein-nucleotide interactions play a central role in the flow of biological information in all living systems. In the immune system, the importance of DNA-binding proteins in the regulation of transcription has been studied extensively. More recently, the importance of RNA-binding proteins (RBPs) in maintenance of homeostasis as well as in shaping the strength and duration of immune responses post-transcriptionally has been noted. In order to gain further insight into the mechanisms of RBP-mediated immune regulation, we are developing tools for nucleotide binding site prediction and flexible protein-nucleotide docking.

## Multiple sequence alignment

## Multiple sequence alignment

Multiple sequence alignment (MSA) is an important step in many comparative analyses of biological sequences and MAFFT is one of the most popular programs for building MSAs. Since the first release of MAFFT in 2002, we have been continuously improving its accuracy, speed and utility in practical situations, and have provided different options for newly emerging types of data and analyses. Recent features include: inclusion of secondary structural information of non-coding RNAs and proteins, interactive selection of sequences for phylogenetic tree inference, etc. We are working on an extension to make more accurate options applicable to a larger number of sequences, responding to the demands of large-scale analyses.





Next-generation sequencing (NGS) is a technology that can generate enormous amount of genomic information in a short time and has made huge progress in genomic science and infectious disease research. Staffs at the Department of Infection Metagenomics who specialized in bioinformatics, microbiology, and infectious diseases gather to conduct research on pathogens and infectious diseases using NGS-based genomic/metagenomic analysis.

Head  
Professor  
**Toshihiro Horii (SUP)**

Professor  
**Tetsuya Iida (SUP)**



### Publication

- (1) Herpes zoster laryngitis in a patient treated with fingolimod. Hagiya H., et al. *J Infect Chemother.* (2016) Aug 20.
- (2) Metagenomic Analysis of Cerebrospinal Fluid from Patients with Multiple Sclerosis. Perlejewski K., et al. *Adv Exp Med Biol.* (2016) 935:89-98
- (3) Lypd8 promotes the segregation of flagellated microbiota and colonic epithelia Okumura R. et al., *Nature.* (2016) Apr 7;532(7597):117-21.
- (4) Homo-trimeric structure of the type IVb minor pilin CofB suggests mechanism of CFA/III pilus assembly in human enterotoxigenic Escherichia coli. Kawahara K. J., et al. *Mol Biol.* (2016) Feb 11.
- (5) Metagenomic Analysis Reveals Dynamic Changes of Whole Gut Microbiota in the Acute Phase of Intensive Care Unit Patients. Ojima M., et al. *Dig Dis Sci.* (2015) Dec 29.
- (6) Performance comparison of second- and third-generation sequencers using a bacterial genome with two chromosomes. Miyamoto M., et al. *BMC Genomics.* (2014) Aug 21;15(1):699.

### Staff

Assoc. Prof. : Naohisa Goto (SUP) / SA Assoc. Prof. : Shota Nakamura (SUP) /  
SA Asst. Prof. : Daisuke Motooka (SUP) / Postdoc. : Yuki Matsumoto

### Development of methods for pathogen detection based on metagenomic analysis

A metagenome is the sum of all genomes of all organisms inhabiting a particular environment. The emergence of NGS has enabled comprehensive analysis of genomic information from large numbers of organisms, thereby leading to significant advances in metagenomic analysis. For example, comprehensive analysis of microbial genomes in blood or nasopharyngeal samples from patients suffering from diseases of unknown cause makes it possible to identify the pathogens causing these symptoms and the genetic factors responsible for pathogenesis. This method, unlike conventional pathogen-specific methods, is applicable to various types of sample (e.g., blood, nasal swab, stool). It can also detect multiple pathogens in a single sample. Our laboratory uses metagenomic analysis to develop new methods for the diagnosis of infectious diseases.

### Genomic analysis of microbial pathogens

The molecular mechanisms underlying the pathogenicity of many infectious diseases remain unclear. Our laboratory conducts genomic analysis-based research to identify genes responsible for pathogenicity and to identify the molecular mechanisms by which infectious diseases develop.



Fig. 1. Large scale computer system for NGS data analysis.

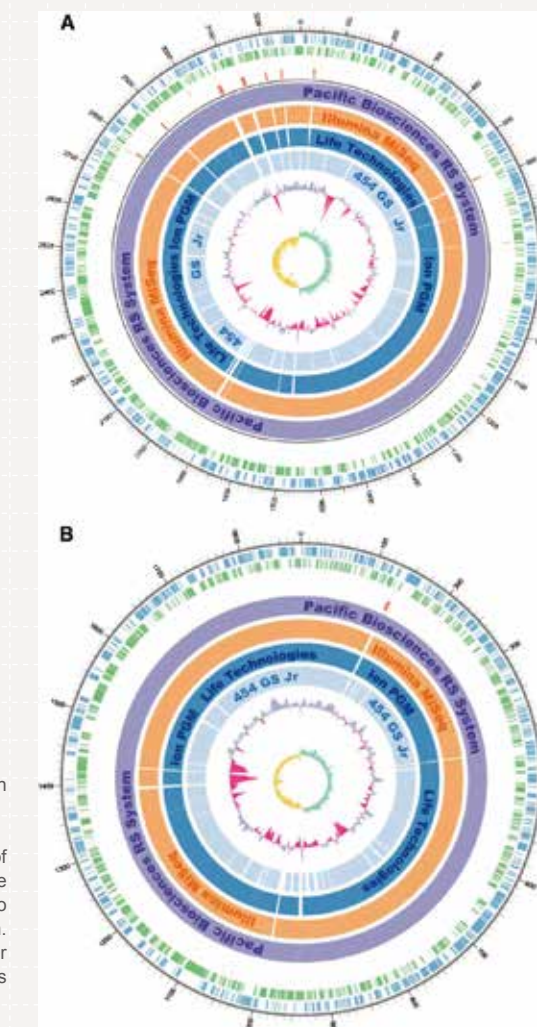
Fig. 2.

Genomic analysis of *Vibrio parahaemolyticus* using four models of next-generation sequencer: 454 GS Jr (Roche), IonPGM (Life Technologies), MiSeq (Illumina), and Pacific Biosciences RS System (PacBio). GS Jr, MiSeq, and IonPGM produce short reads. Therefore, they require assembly of short fragments. The third generation sequencer, PacBio, on the other hand can produce long reads and assemble them into two long sequences with lengths equivalent to two chromosomes. However, PacBio has low accuracy with respect to sequence information. Although the read length of MiSeq is far shorter than that of PacBio, it has a much higher yield. Thus, to conduct a proper analysis it is necessary to understand the characteristics of each sequencing platform.

### Study of gut flora during onset of infectious disease

It is becoming clear that the gut flora is microbiota that is involved in various diseases and plays an important role in host defense. By performing metagenomic analysis of changes in and recovery of bacterial gut flora over time in cases of diarrhea, our laboratory is studying the relationship between human gut flora and pathogens. Furthermore, not only is bacterial gut flora related to disease, but it is also closely related to lifestyle factors. Our research is focused on how bacterial gut flora is affected by environmental factors and the physiological state of the individual.

NGS technology had made remarkable progress. New hardware platforms are being developed. NGS itself reads only nucleic acid sequences, and further analysis is required to handle the enormous amount of data obtained. It is important to have a broad knowledge of bioinformatics, microbiology, and genomics in order to select the appropriate model based on the characteristics of each sequencing platform. At our laboratory, we carry out co-operative research with specialists in the fields of bioinformatics, microbiology, and infectious diseases.





Associate Professor  
Takeshi Miwa

## Profile

Dr. Takeshi Miwa received his Ph.D. from Osaka University in 1983. He appointed as a Assoc. prof. in RIMD after working at The University of Tokyo and Stanford University.

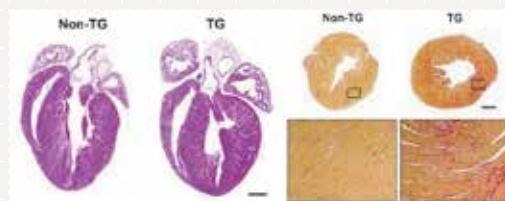
## Publication

- (1) Connexin45 contributes to global cardiovascular development by establishing myocardial impulse propagation. Nishii K., et al. *Mech Dev.* (2016) 140:41-52
- (2) A novel heart failure mice model of hypertensive heart disease by angiotensin II infusion, nephrectomy, and salt loading. Tsukamoto Y., et al. *Am J Physiol Heart Circ Physiol.* (2013) 305:1658-67
- (3) Interleukin-16 promotes cardiac fibrosis and myocardial stiffening in heart failure with preserved ejection fraction. Tamaki S., et al. *PLoS One* (2013) 8(7):e68893
- (4) L-Carnitine prevents the development of ventricular fibrosis and heart failure with preserved ejection fraction in hypertensive heart disease, Omori Y., et al. *J Hypertens.* (2012) 30:1834-44

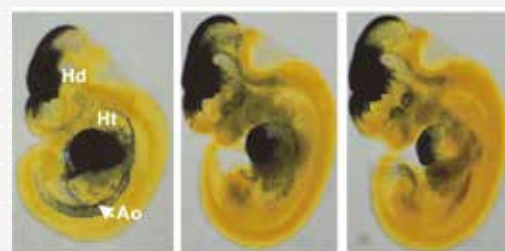
We are currently using animal models to investigate the molecular biological mechanisms involved in human disease, particularly cardiovascular disease.

1) We have established a diastolic heart failure model using Dahl salt-sensitive rats. This model showed that left ventricular (LV) fibrosis and stiffening play crucial roles in the development of heart failure with preserved ejection fraction (HFpEF). Digitalis-like factors and the subsequent activation of the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger may play important roles in the development of hypertensive HFpEF and also regulate the effect of carnitine when administered to the HFpEF model. In addition, serum interleukin-16 (IL-16) levels are elevated both in patients with HFpEF and in the rat model. Increased cardiac expression of IL-16 in transgenic mice induces cardiac fibrosis and LV myocardial stiffening, which is accompanied by increased macrophage infiltration (Fig. 1).

2) To understand the cellular and molecular aspects of vascular smooth muscle (SM) cell growth in atherosclerotic plaques, we characterized the mechanisms responsible for transcription of SM-specific genes, particularly the human SM alpha-actin (SmaA) gene (Fig. 2). Several cis-acting DNA elements and transcriptional nuclear factors essential for SmaA expression have been identified. Since SmaA is also expressed in many tissues during acute inflammation, we are examining expression of the SmaA and its function(s).



**Fig. 1.** Increased cardiac expression of IL-16 in mice under control of the α-MHC promoter causes increased myocardial fibrosis and stiffness. (Left) Four-chamber view of hearts from non-transgenic and transgenic mice. (Right) Sirius Red-stained sections of the LV from fibrotic areas.



**Fig. 2.** Embryonic aorta (Ao) express the human vascular SM α-actin promoter (left), but those with -1M (center) and 4M (right) point mutations in the transcriptional nuclear factor-binding regions do not.

To prevent and control infectious diseases, it is essential to understand both the mechanisms of pathogenicity as well as host immune responses. The NGS Core Facility of the Genome Information Research Center was founded to support and provide genomic technologies for research on infectious diseases and immunology. We are supporting researchers in analyzing large volumes of data obtained from NGS and DNA microarrays by combining bioinformatics approaches with large computing systems designed for big data. Recently, we have begun supporting activities outside of infectious disease research for researchers from Osaka University as well as other universities.

## Advanced NGS Instruments

In the last decade, as a result of the remarkable technological innovation of NGS systems, which can read a massive number of sequences simultaneously and at high speed, we are now able to analyze genomic information quickly and at low cost. Various NGS instruments including IonPGM (Life Technologies), MiSeq, HiSeq (Illumina), and PacBio RSII (Pacific Biosciences) are available in our Core Facility. We provide genomics applications according to researchers' needs in addition to training courses covering topics such as NGS procedures as well as other related experimental technologies. Furthermore, we are expanding research with the aim of improving bioinformatics analysis in collaboration with the Department of Genome Informatics and the Department of Infection Metagenomics.

## Publication

- (1) Phenotype-genotype correlations of PIGO deficiency with variable phenotypes from infantile lethality to mild learning difficulties. Tanigawa J., et al. *Hum Mutat.* (2017) Mar 23. In press.
- (2) Quasispecies of Hepatitis C Virus Participate in Cell-Specific Infectivity. Fukuhara T., et al. *Sci Rep.* (2017) Mar 22;7:45228.
- (3) Polarization of M2 macrophages requires Lamtor1 that integrates cytokine and amino-acid signals. Kimura T., et al. *Nat Commun.* (2016) Oct 12;7:13130.
- (4) Microarray and whole-exome sequencing analysis of familial Behçet's disease patients. Okuzaki D., *Sci Rep.* (2016) Jan 20;6:19456.

Next-Generation Sequencing (NGS)  
Core Facility

## Staff

Prof. (SUP) : Tetsuya Iida, Ph.D.  
SA Assoc. Prof. (SUP) : Shota Nakamura, Ph.D.  
Asst. Prof. : Daisuke Okuzaki, Ph.D.  
SA Asst. Prof. (SUP) : Daisuke Motooka, Ph.D.



Next Generation Sequencer HiSeq



Large-scale computer system for NGS

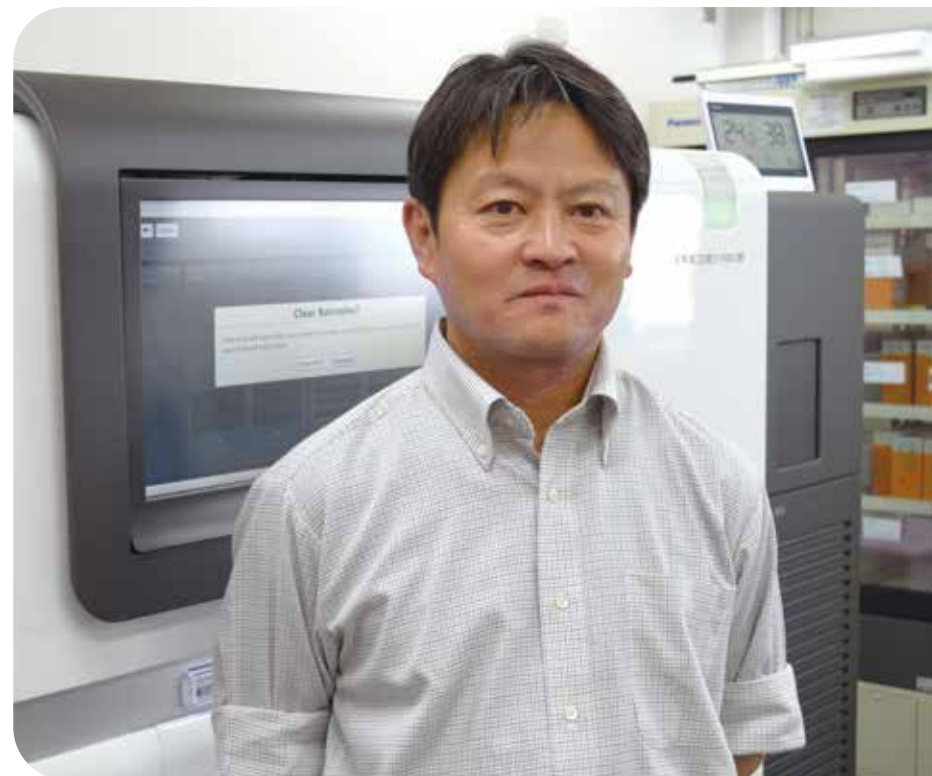


In our laboratory, we are conducting research and collecting genomic information to understand how bacterial pathogens infect the host and cause disease. In addition, by developing new pathogen detection methods using high-throughput DNA sequencers, we aim to identify novel pathogens and reveal the pathogenesis of unknown infectious diseases.

## Professor Tetsuya Iida

### Profile

Dr. Iida received his Ph.D. from Osaka University in 1991. He was appointed SA Professor at the International Research Center for Infectious Diseases in RIMD after working as a Research Associate for six years and an Associate Professor for seven years. He took his current position as a Professor of RIMD in 2015.



### Publication

- (1) A repeat unit of *Vibrio* diarrheal T3S effector subverts cytoskeletal actin homeostasis via binding to interstrand region of actin filaments. Nishimura M., et al. *Sci Rep.* (2015) 5:10870.
- (2) Interaction between the type III effector VopO and GEF-H1 activates the RhoA-ROCK pathway. Hiyoshi H., et al. *PLoS Pathog.* (2015) 11(3):e1004694.
- (3) A cytotoxic type III secretion effector of *Vibrio parahaemolyticus* targets vacuolar H<sup>+</sup>-ATPase subunit c and ruptures host cell lysosomes. Matsuda S., et al. *PLoS Pathog.* (2012);8(7):e1002803.
- (4) VopV, an F-actin-binding type III secretion effector, is required for *Vibrio parahaemolyticus*-induced enterotoxicity. Hiyoshi H., et al. *Cell Host Microbe.* (2011) 10(4):401-9. doi: 10.1016/j.chom.2011.08.014.
- (5) Metagenomic diagnosis of bacterial infections. Nakamura S., et al. *Emerg Infect Dis.* (2008) 14(11):1784-6.
- (6) Genome sequence of *Vibrio parahaemolyticus*: a pathogenic mechanism distinct from that of *V. cholerae*. Makino K., et al. *Lancet.* (2003) 361(9359):743-9.

## Staff

Assoc. Prof. : Toshio Kodama /  
Asst. Prof. : Shigeaki Matsuda / Grad. Student 3

## Identifying the mechanism(s) underlying bacterial infection and pathogenesis

We performed whole genome sequencing of *Vibrio parahaemolyticus*, a bacterium that causes acute gastroenteritis in humans, and revealed that the type III secretion system T3SS2 is essential for pathogenicity. T3SS2 directly injects bacterial proteins (effectors) into target host cells. We demonstrated that injection of those effectors by T3SS2 from *V. parahaemolyticus* leads to inflammation of the intestinal mucosa and diarrhea. Currently, we are analyzing the molecular mechanism by which those effectors cause the symptoms of acute gastroenteritis.

Also, we revealed that expression of the genes encoding T3SS2 is induced by bile. In fact, chemical substances that adsorb and remove bile suppressed symptoms caused by *V. parahaemolyticus* in animal models, suggesting that these substances may be new therapeutic agents for *V. parahaemolyticus* infection. This is an example of “anti-virulence therapy” rather than antimicrobial therapy. This kind of

approach is expected to provide novel therapeutic strategies for various bacterial infections. Furthermore, based on findings obtained from our research on pathogenicity, we aim to explore the life cycle of bacterial pathogens in their natural environments.

## Development of methods to diagnose bacterial infections based on genomics and metagenomics

Emerging and re-emerging infectious diseases cause many problems worldwide. In many cases of such infection, the causative agent is unknown and/or the pathogenic mechanism is not yet clear. To identify the agents that cause such infections, and to understand the underlying pathogenesis, we are developing a high-throughput DNA sequencing-based system to detect pathogens and analyze their virulence traits.

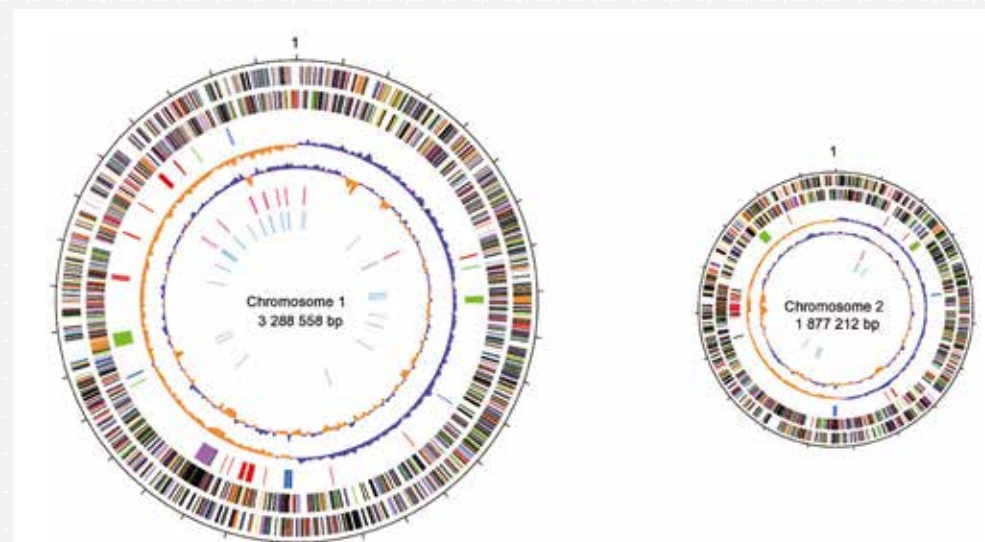


Fig. 1. The genomes of bacteria belonging to genus *Vibrio* comprise two distinct circular chromosomes.

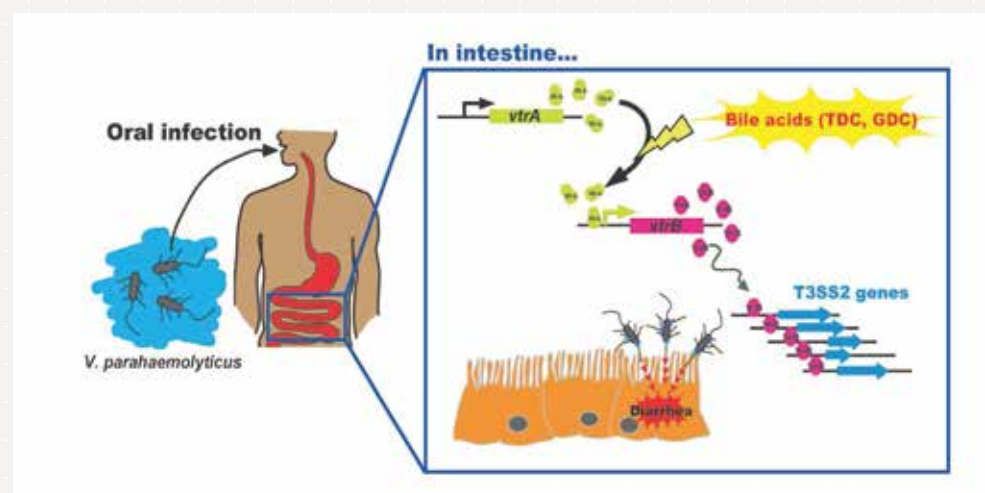


Fig. 2. Bile in the small intestine induces expression of genes encoding T3SS2, which is the major virulence factor produced by *Vibrio parahaemolyticus*, the causative agent of diarrhea.



Malaria is widespread in tropical and subtropical regions, and millions of people, particularly in Africa, remain at risk of disease and death despite substantial progress in malaria control. No effective malaria vaccine has been developed or licensed. Our laboratory is undertaking basic research and conducting clinical trials on our own candidate vaccine antigen gene.

## Professor Toshihiro Horii (SUP)

### Profile

Dr. Horii received his Ph.D. from Osaka University in 1981. After working at the Faculty of Science in Osaka University as Research Associate, he was appointed Associate Professor at RIMD in 1991 and became Professor in 1999.



### Publication

- (1) Antibody titres and boosting after natural malaria infection in BK-SE36 vaccine responders during a follow-up study in Uganda. Yagi M., et al. *Sci Rep.* (2016) 6:34363. doi: 10.1038/srep34363.
- (2) Immunogenicity and protection from malaria infection in BK-SE36 vaccinated volunteers in Uganda is not influenced by HLA-DRB1 alleles. Tougan T., et al. *Parasitol Int.* (2016) 65 (5 Pt A):455-8.
- (3) Protective epitopes of the *Plasmodium falciparum* SERA5 malaria vaccine reside in intrinsically unstructured N-terminal repetitive sequences. Yagi M., et al. *PLoS One* (2014) 9(6):e98460.
- (4) Phase 1b randomized trial and follow-up study in Uganda of the blood-stage malaria vaccine candidate BK-SE36. Palacpac N. M., et al. *PLoS One* (2013) 8(5):e64073.
- (5) *Plasmodium falciparum* serine repeat antigen 5 (SE36) as a malaria vaccine candidate. Palacpac N. M., et al. *Vaccine* (2011) 29(35):5837-45.
- (6) Evidences of protection against blood-stage infection of *Plasmodium falciparum* by the novel protein vaccine SE36. Horii T., et al. *Parasitol Int.* (2010) 59(3):380-6.

### Staff

Asst. Prof. : Nobuko Arisue / Asst. Prof. : Takahiro Tougan /  
Postdoc. : Edula Jyotheeswara Reddy / Guest Prof. : Eisaku Kimura

## Malaria vaccine targeting SERA5

The treatment of malaria patients is completely dependent on the efficacy of anti-malaria drugs; however, drug-resistant parasites are emerging. Although a malaria vaccine is the ideal weapon against this pathogen, vaccine development is hampered by genetic polymorphisms in candidate antigen genes.

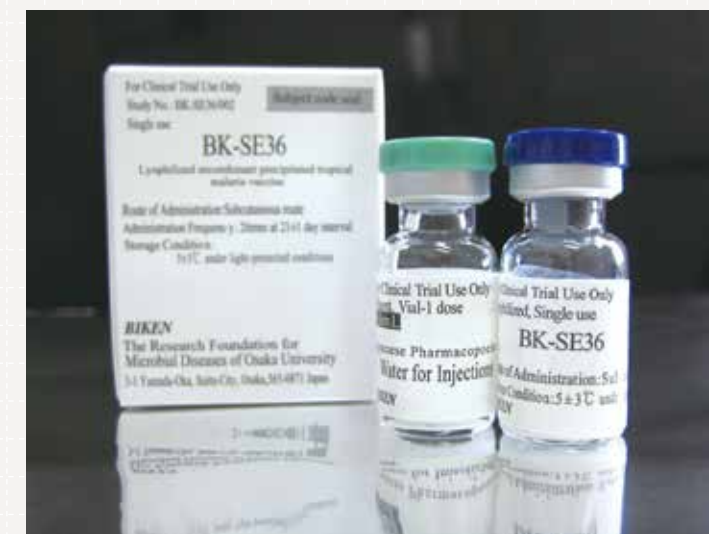
We have been focusing on the SERA5 molecule of *P. falciparum* (the malaria parasite) and developed malaria vaccine BK-SE36 by utilizing a recombinant SERA5 protein. SERA5 is a protein that is highly expressed/produced in large amounts during parasite growth in red blood cells. Epidemiological studies in malaria hyper-endemic areas showed that children with antibodies against SERA5 experienced few or no symptomatic/clinical malaria, albeit such children are a minority.

It was surprising that Ugandan adults that suffered numerous malaria infections did not respond to vaccination with BK-SE36. By contrast, malaria-naïve Japanese adults produced high levels of antibodies. Moreover, in young Ugandan children that experienced few malaria episode, we

observed good antibody response. we obtained 72% protective efficacy 1 year post-2nd-vaccination in a follow-up study of 6-20 years old in the phase Ib trial. This suggests that our vaccine provides better protection in younger individuals. We are currently conducting Phase Ib clinical trials in Burkina Faso West Africa involving toddlers aged 1–5 years.

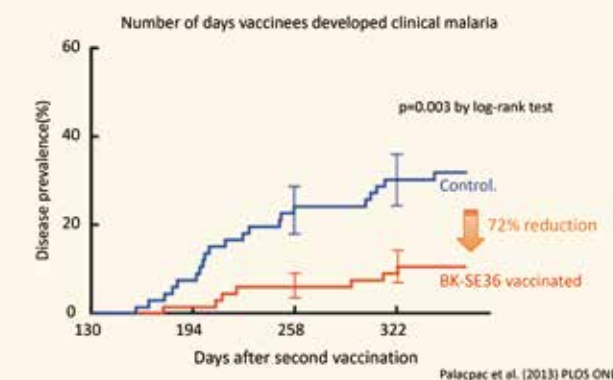
## Molecular mechanism underlying the use of antigenic genes to treat malaria

The malaria parasite develops highly sophisticated strategies to evade the human immune system. One of the most difficult phenomena encountered by those developing vaccines is genetic polymorphism of vaccine candidate genes; that is, field-isolated parasites harbor different sequences from the vaccine candidate genes. Fortunately, SERA5 is highly homologous among malaria parasites worldwide. We have been undertaking genetic analysis of SERA5 epitopes and formulating new vaccines with novel adjuvants to ensure better efficacy.



**Fig. 1. Clinical trial of the BK-SE36 malaria vaccine.**  
The vaccine was produced under GMP (Good Manufacturing Practice) conditions at the Kanonji Institute of The Research Foundation for Microbial Diseases of Osaka University.

### Protective effect against symptomatic/clinical malaria in BK-SE36 vaccinees

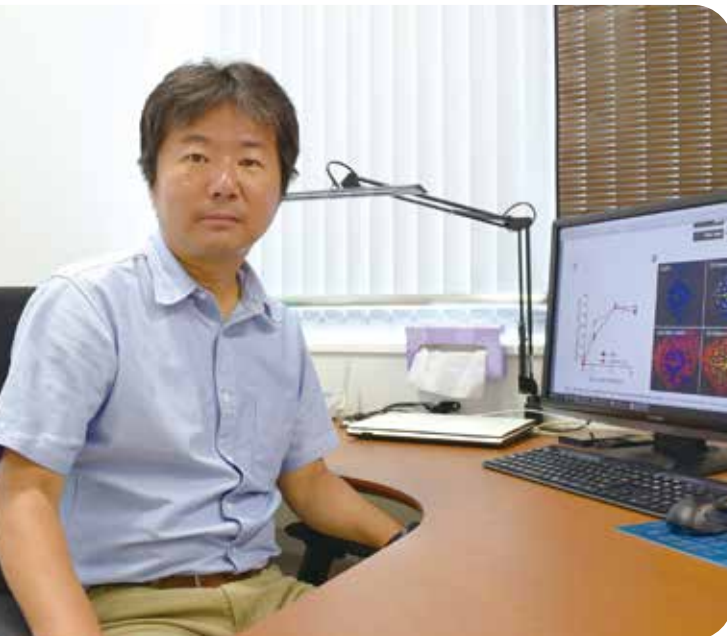


**Fig. 2.**  
Kaplan-Meier curves for 6- to 20-year-olds at 130–365 days post-second vaccination with BK-SE36. Comparison of the number of days from 130–365 days after second vaccination that 6–20 year-old BK-SE36 vaccinees and control grouped developed clinical malaria.



## Staff

Assis. Prof. : Yuta Kanai /  
Postdoc. : Takahiro Kawagishi /  
Grad. Student 2

Associate Professor  
Takeshi Kobayashi

## Profile

Dr. Kobayashi received his Ph.D. from Osaka University in 2000. He became a Research associate at RIMD in the same year. He spent for five years as a postdoctoral fellow in Vanderbilt University, USA before returning to Japan to work at the Institute for Virus Research in Kyoto University. He was appointed SA Associate Professor of RIMD in 2012. He is in his current position from 2016.

## Publication

- (1) Entirely plasmid-based reverse genetics system for rotaviruses. Kanai Y, Komoto S, Kawagishi T, Nouda R, Nagasawa N, Onishi M, Matsuura Y, Taniguchi K, Kobayashi T. *Proc Natl Acad Sci U S A*. 2017 Feb 28;114(9):2349-2354.
- (2) Reverse genetics for fusogenic bat-borne orthoreovirus associated with acute respiratory tract infections in humans: role of outer capsid protein sigmaC in viral replication and pathogenesis. Kawagishi T, et al. *PLoS Pathog*. (2016) 12:e1005455
- (3) Rapid whole genome sequencing of Miyazaki-Bali/2007 Pteropine orthoreovirus by modified rolling circular amplification with adaptor ligation - next generation sequencing. Singh H., et al. (2015) *Sci. Rep.* 5:16517
- (4) Imported case of acute respiratory tract infection associated with a member of species Nelson Bay Orthoreovirus. Yamanaka Y., et al. (2014) *PLoS One* 9:e92777

## 1) Rotaviruses (RVs)

RVs are highly important pathogens that cause severe diarrhea in infants and young children worldwide. Understanding of the molecular mechanisms underlying the replication and pathogenesis of RVs has been hampered by the lack of a reverse genetics system that allows the synthesis of recombinant viruses from artificial genes. Recently, we developed a long-awaited plasmid-based reverse genetics system for RVs. This technique opens up new horizons for studying the replication and pathogenesis of RVs. We are investigating RV biology and developing vaccines and therapeutics using a combination of genetic, biochemical, and biophysical approaches.

## 2) Oncolytic viral therapy using reoviruses

Mammalian orthoreoviruses (reoviruses) are members of the family *Reoviridae* and have a genome containing 10 segments of double-stranded (ds) RNA. Reoviruses are highly tractable experimental models for studying the replication and pathogenesis of dsRNA viruses. In the last decade, reoviruses have been evaluated as oncolytic agents against a variety of tumors, including head and neck, colon, breast, and pancreatic cancers, in animal models and humans. This is based on the observation that reoviruses induce cell death and apoptosis in tumor cells with an activated Ras signaling pathway. Wild-type reovirus-based oncolytic therapies are safe, but their efficacy is currently limited. We are developing safer and more effective reovirus-based cancer

therapeutics by genetic modification.

## 3) Highly pathogenic bat-borne reovirus

Nelson Bay reovirus (NBV) was isolated from a flying fox in 1968 but had not been associated with any disease. However, NBVs were recently isolated from human patients suffering from acute respiratory tract infections in Malaysia, Indonesia, China, and Japan. These isolates have given rise to increasing concerns about bat-transmitted reovirus infections in humans. We are investigating how NBV replicates and causes disease *in vitro* and *in vivo*.

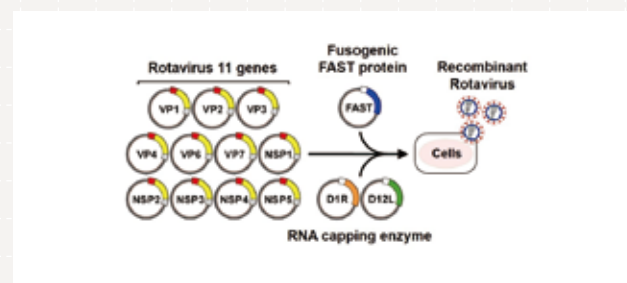


Fig Generation of RVs from Cloned cDNAs

## Staff

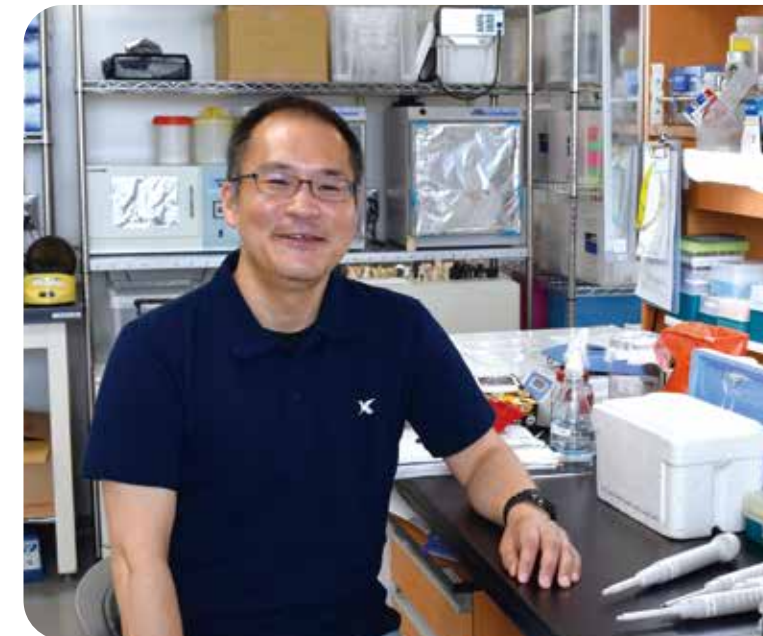
SA Assis. Prof. : Akatsuki Saito /  
Postdoc. : Yutaka Terada /  
Grad. Student 2

## Profile

Dr. Kamitani received his Ph.D. from Osaka University in 2003. After working at RIMD for one year, he spent the period from 2004 to 2009 as a postdoctoral fellow at the University of Texas Medical Branch at Galveston. He returned to the RIMD and became an Associate professor for Global COE program. He took his current position in 2013.

## Publication

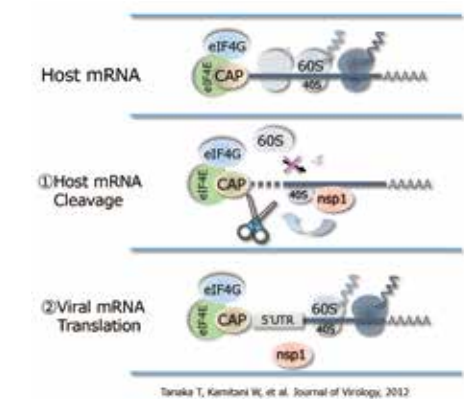
- (1) Nonstructural protein p39 of feline calicivirus suppresses host innate immune response by preventing IRF-3 activation. Yumiketa Y., et al. *Vet. Microbiol.* (2016) 185:62-7
- (2) Japanese encephalitis virus core protein inhibits stress granule formation through an interaction with Caprin-1 and facilitates viral propagation. Katoh H., et al. *J. Virol.* (2013) 87(1):489-502
- (3) Severe Acute Respiratory Syndrome Coronavirus nsp1 Facilitates Efficient Propagation in Cells through a Specific Translational Shutoff of Host mRNA. Tanaka T, et al. *J. Virol.* (2012) 86(20):11128-37

Guest Associate Professor  
Wataru Kamitani

Coronaviruses infect many different animals, including human, and cause them to have respiratory and gastrointestinal diseases. Newly emerged Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) infect respiratory tract and cause severe pneumonia disease. Our research group focuses on these coronaviruses and studies the molecular biology and host cell-virus interaction of these coronaviruses.

SARS-CoV is the etiological agent of a newly-emerged human respiratory disease that originated in southern China in 2002 and spread worldwide in the 2003 epidemic. After 10 years of the epidemic of SARS-CoV, novel coronavirus, MERS-CoV, has been reported in Middle East region. MERS-CoV spreads to North America, Europe, China, and Korea. No effective treatment against MERS-CoV. Our research group studies about non-structural protein 1 (nsp1), that is one of pathogenicity factor in Coronavirus. Nsp1 of SARS-CoV induces host protein synthesis suppression through binding to 40S ribosome complex. The nsp1 enhance viral replication through binding to viral RNA. Our research group utilizes a Bacterial Artificial chromosome (BAC)-based revers genetics system for these coronaviruses. Our group try to understand the mechanism

of Coronaviruses replication and pathogenesis for development therapeutic targets against Coronaviruses using the BAC-based revers genetics system.



**Fig. Gene expression control by SARS-CoV nsp1**  
① Nsp1 binds to 40S ribosome, and then induces translational shutoff. The nsp1-40S binding induces cleavage of mRNA.  
② Nsp1 binds to viral mRNA, and then the interaction enhances viral replication.



International Research Center for  
Infectious Diseases

Pathogenic Microbes  
Repository Unit

### Staff

Head (SUP): Tetsuya Iida, Ph.D.  
Associate Professor (SUP): Toshio Kodama, Ph.D.

The facility is part of the National BioResource Project (NBRP) directed by the Ministry of Education, Culture, Sports, Science and Technology, Japan, and is a member of the Japan Society for Culture Collections (JSCC); therefore, we collect and preserve pathogenic bacterial strains. These strains are distributed to investigators in and outside this country upon request. Our collection is listed on the website for this facility (<http://rceid.biken.osaka-u.ac.jp>) and that of the NBRP.



Germ Cell Group

Assoc. prof.  
**Masami Nozaki**



### Profile

Dr. Nozaki received his Ph.D. from Osaka University in 1986. He took his current position at RIMD in 2007 after working as a Research Associate and an Associate Professor in the same institution.

### Publication

- (1) Lapatinib-resistant cancer cells possessing epithelial cancer stem cell properties develop sensitivity during sphere formation by activation of the ErbB/AKT/cyclin D2 pathway. Ohnishi Y., et al. *Oncol Rep* (2016) 36 (5):3058-64.
- (2) Cetuximab-resistant oral squamous cell carcinoma cells become sensitive in anchorage-independent culture conditions through the activation of the EGFR/AKT pathway. Ohnishi Y., et al. *Int J Oncol.*(2015) 47(6):2165-72.
- (3) Interaction between basigin and monocarboxylate transporter 2 in the mouse testes and spermatozoa. Chen C., et al. *Asian J Androl* (2016) 18 (4):600-6.
- (4) Isolation and propagation of neural crest stem cells from mouse embryonic stem cells via cranial neurospheres. Minamino Y., et al. *Stem Cells Dev* (2015) 24 (2):172-81.

Our body is derived from a single fertilized egg. During development, germ cells (and sometimes cancer cells), as well as many types of tissues, are generated. We in the germ cell group have been conducting research focusing on germ cells, the early embryo, stem cells, and cancer cells. Currently, we study osteogenesis from pluripotent stem cells and are characterizing cancer stem cells.

Neural crest cells are derived from neuroepithelium via epithelial-mesenchymal transition (EMT) at the early developmental stage. These cells migrate extensively and differentiate into various tissues in the whole embryo. Bone is generated from mesoderm; however, most of the skull is derived from neural crest cells. Recently, we established a method of differentiating ES cells into maxillofacial bone via neural crest cells. We are conducting research aimed at applying our findings to regenerative medicine using iPS cells, adult tissue stem cells, and ES cells.

EMT is a phenomenon also observed in malignancy. Epithelial cell-derived cancer cells acquire migration and invasive potency after EMT, leading to metastasis. Some malignant cancer cells have stem cell-like properties. Differences in the characteristics of cancer stem cells and other cancer cells make the disease difficult to treat. Thus, our aim is to understand the characteristics of cancer stem cells and establish new treatment strategies.

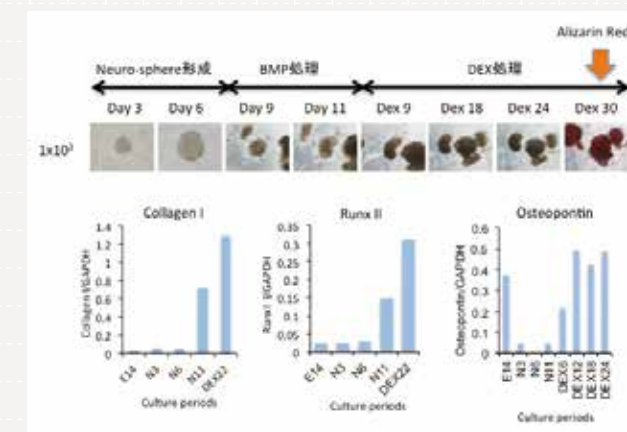


Fig. Neuro-spheres derived from ES cells are induced to undergo osteogenesis by treatment with BMP4 and DEX. Calcium deposition is shown by red-staining of alizarin, and upregulation of osteogenic marker genes during osteogenesis is detected by semi-quantitative RT-PCR.



Glycosylphosphatidylinositol (GPI) is a glycolipid attached to proteins and anchors them onto the plasma membrane. GPI-anchored protein has various and important physiological functions in our body. Why proteins have this peculiar structure like GPI? Our research goal is to elucidate biogenesis, transport and remodeling of GPI-anchored proteins and understand its physiological significance in our body.

## Endowed Chair Professor Taroh Kinoshita

### Profile

Dr. Kinoshita received Ph.D. from Osaka University in 1981. After working at Department of Bacteriology, Osaka University Medical School and Department of Pathology, New York University School of Medicine, he appointed as a Professor in RIMD in 1990. He served as a Director of RIMD from 2003 to 2007. He concurrently serves as a Professor in Osaka University Immunology Frontier Research Center from 2007. From 2017, he is in the current position.



## Endowed Chair Professor Yoshiko Murakami

### Profile

Dr. Murakami received Ph.D. from Osaka University in 2001. After working at Osaka University Hospital and Hyogo Prefectural Nishinomiya Hospital, she joined Dept. of Immunoregulation at RIMD in 1998. She became an Associate professor for Office of Combined Program on Microbiology and Immunology (concurrently serve for Dept. of Immunoregulation and Immunoglycobiology in IFReC) in 2009. She is in the current position from 2017.



### Publication

- (1) A GPI processing phospholipase A2, PGAP6, modulates Nodal signaling in embryos by shedding CRIPTO. Lee, G-H., et al. *J. Cell Biol.* (2016) 215:705-718.
- (2) Pathogenic variants in PIGG cause intellectual disability with seizures and hypotonia. Makrythanasis, P., et al. *Am. J. Hum. Genet.* (2016) 98:615-626.
- (3) Post-Golgi anterograde transport requires GARP-dependent endosome-to-TGN retrograde transport. Hirata, T., et al. *Mol. Biol. Cell* (2015) 26:3071-3084.
- (4) The alpha helical region in p24y2 subunit of p24 cargo receptor is pivotal for the recognition and transport of glycosylphosphatidylinositol-anchored proteins. Theiler, R., et al. *J. Biol. Chem.* (2014) 289:16835-16843.
- (5) Null mutation in PGAP1 impairs GPI-anchor maturation in patients with intellectual disability and encephalopathy. Murakami, Y., et al. *PLoS Genet.* (2014) 10(5):e1004320.
- (6) Glycosylphosphatidylinositol (GPI) anchor deficiency caused by mutations in PIGW is associated with West syndrome and hyperphosphatasia with mental retardation syndrome. Chiyonobu, T., et al. *J. Med. Genet.* (2014) 51:203-207.

### Staff

Postdoc. : Lee Gunhee / Grad. Student 1

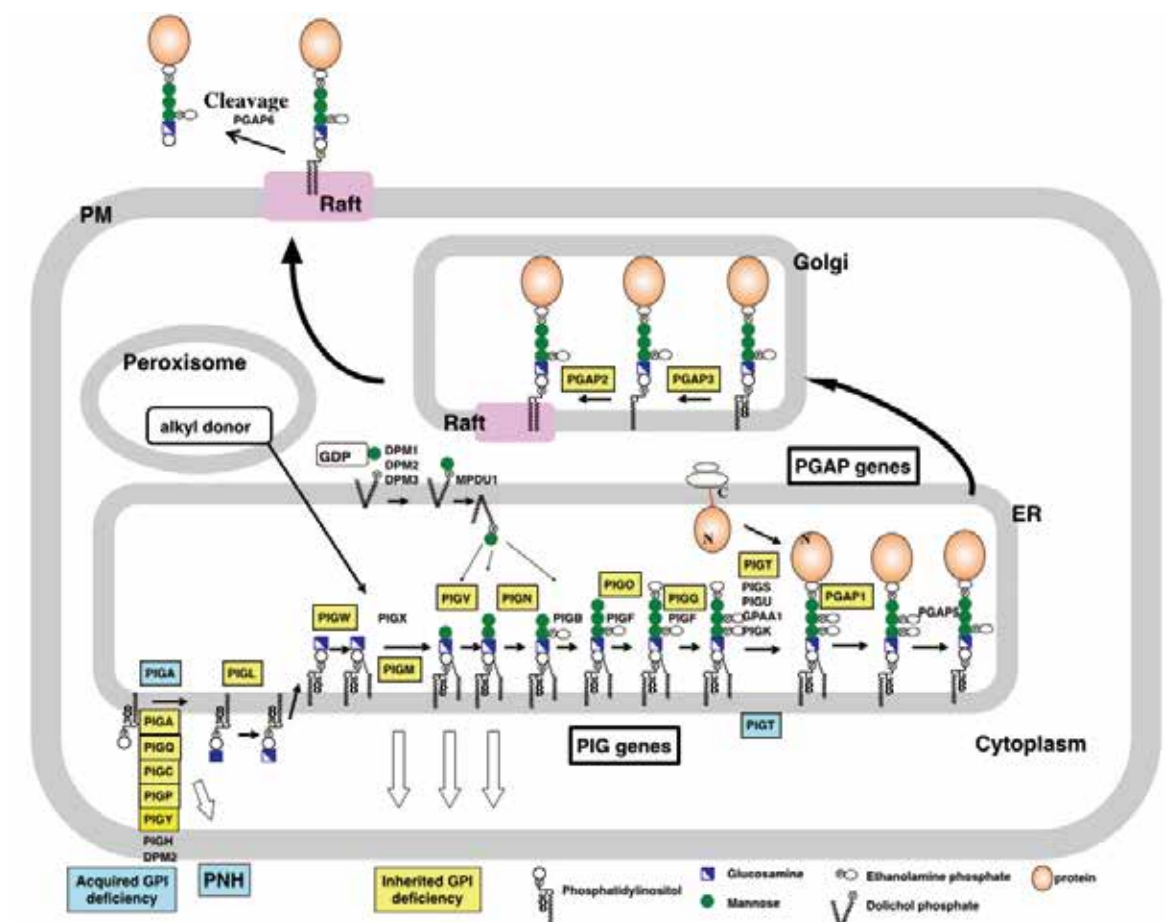
## How are GPI-anchored proteins (GPI-APs) regulated?

GPI anchors are synthesized in the endoplasmic reticulum and attached to the C terminus of proteins during posttranslational modification. GPI-anchored proteins are transported from the endoplasmic reticulum to the Golgi and further to the cell surface in a way that is regulated according to the features of GPI. Recently, we identified the enzyme that can cut GPI-anchors, and showed GPI-APs can be secreted and work in the tissues distant from its origin. This result indicates that GPI anchors enable our body system to regulate where and when the protein works in a various way. We are currently studying the molecular mechanism to control the functions of GPI-APs. In addition, GPI anchor has specific carbohydrate side-chains and intriguingly, the chain varies among cells and proteins. We are interested in the physiological significance of this carbohydrate chain and asking how this chain is synthesized in our cells.

## Molecular mechanisms of GPI deficiencies.

We found that paroxysmal nocturnal hemoglobinuria (PNH) is caused by somatic mutation of the X-linked PIGA gene, a gene for GPI-anchor biosynthesis. A recent report showed that atypical PNH is caused by somatic mutation of one allele of the PIGT gene, a gene for GPI-anchor attachment, in combination with a germline mutation in the other allele. Now, we are studying how unused GPI-anchor is involved in pathogenesis of atypical PNH and try to find a cure for this disease.

We also identified a disease called inherited GPI deficiency (IGD) caused by the mutation of the GPI-anchor synthesizing enzyme, PIGM. The recent whole exome sequencing analysis using the next generation sequencer revealed 16 GPI-related gene mutations responsible for IGD. To elucidate the molecular mechanisms of the pathogenesis of this disease, we developed the system to analyze GPI biosynthesis and modification. This system contributes to the IGD research in all over the world. Our aim is to elucidate how GPI-anchors are involved in IGD and find the way to overcome this disease.



GPI-anchor biosynthesis and the transport/remodeling of GPI-APs.



Until recently, it was believed that infectious diseases could be conquered by developing chemotherapy regimens and vaccines; however, the recent worldwide emergence of new infectious diseases and the re-emergence of infectious diseases once considered to be under control have seriously challenged this notion. Since many infectious diseases spread rapidly across national borders, it is clear that they cannot be controlled by the efforts of individual countries.

To overcome this, Osaka University founded the Research Collaboration Center on Emerging and Re-emerging Infections (RCC-ERI) at the Thai National Institute of Health (NIH), Department of Medical Sciences, Ministry of Public Health of Thailand, in 2005. The program is now in the third phase (2015–2020) and is sponsored by the Japan Agency for Medical Research and Development, which succeeded to the second phase program named “the Japan Initiative for

Global Research Network on Infectious Diseases (J-GRID).”

In addition to basic and applied research into emerging and re-emerging infections, we aim to develop human resources. We also aim to establish an effective system that would (i) provide information that would help prevent the spread of emerging and re-emerging infections, and (ii) promptly activate a variety of countermeasures should such a disease emerge, including the development of therapeutics and/or vaccines. Finally, we wish to enter into collaboration with laboratories from nations that neighbor Thailand so that we can be on the “frontline,” with the capacity to respond quickly to the global spread of infectious disease.



The collaboration center is located in the campus of the Ministry of Public Health.



BSL-2 and BLS-3 laboratories in the center.

### Kazuhisa Okada Profile

Dr. Okada received his Ph.D. from Osaka university in 2005 and joined RIMD as a postdoctoral fellow in that same year. He was appointed Lecturer of Thailand-Japan Research Collaboration Center on Emerging and Re-emerging infections in 2015 after working as a Post-doctoral fellow from 2005 to 2011 and an Asistant Professor from 2011 to 2015 in the same institution.

### Publication

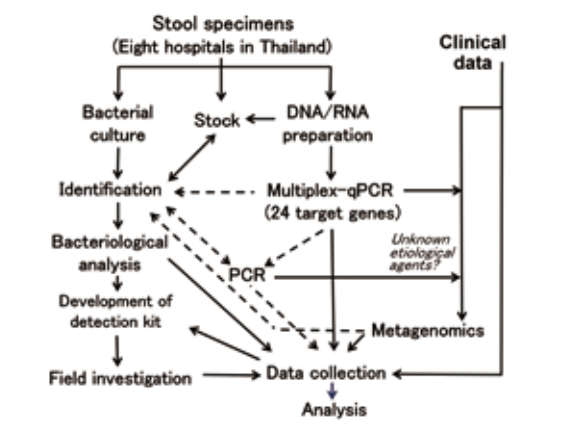
- (1) Characterization of 3 Megabase-Sized Circular Replicons from *Vibrio cholerae*. Okada K., et al. *Emerg Infect Dis.* (2015) 21(7):1262-3.
- (2) Cholera in Yangon, Myanmar, 2012-2013. Aung WW., et al. *Emerg Infect Dis.* (2015) 21(3):543-4.
- (3) Comparative genomic characterization of a Thailand–Myanmar isolate, MS6, of *Vibrio cholerae* O1 El Tor, which is phylogenetically related to a “US Gulf Coast” clone. Okada K., et al. *PLoS One.* (2014) 9 (6):e98120.
- (4) *Vibrio cholerae* O1 isolate with novel genetic background, Thailand–Myanmar. Okada K., et al. *Emerg Infect Dis.* (2013) 19:1015-7.

SA Professor  
**Shigeyuki Hamada (SUP)**  
SA Associate Professor  
**Kazuhisa Okada**



Enteric infectious diseases caused by various microbes occur frequently in Thailand. However, there are no large-scale epidemiological studies of the etiology of gastroenteritis in Thailand. In the Section of Bacterial Infections, we are trying to develop effective diagnostic tools to detect bacterial pathogens and devise measures to prevent enteric infections, including those mediated by *Vibrio cholerae* O1.

We collect and analyze fecal specimens from patients with severe diarrhea admitted to leading hospitals located in different parts of Thailand. We then try to detect specific pathogens by real-time PCR analysis of bacterial genes and culture analysis. We also attempt to identify unknown pathogens using TOF-MS or NGS. In cases of cholera in Thailand or Myanmar, we will co-operate with governmental authorities to analyze *V. cholerae* isolates to elucidate the route of transmission. We will also undertake molecular and/or genomic characterization of any identified pathogen. Our research goals are to develop methods for rapid diagnosis and to prepare countermeasures against what is still a challenging pathogen.



Flow chart to detect “pathogenic” agents from stool specimens of inpatients with acute severe diarrhea and control subjects using multiplex real time PCR and cultural methods. Eight hospitals in different parts of Thailand participate in this study.



SA Professor  
**Masashi Tatsumi (SUP)**



**Profile**

Dr. Tatsumi received his Ph.D. from The University of Tokyo. After working at National Institute of Health in Japan, Pasteur Institute and INSERM (French National Institute of Health and Medical Research) in France, he spent 12 years in National Institute of Infectious Diseases. After retirement, he served as a chief advisor for JICA until taking his current position at RIMD in 2016.

**Publication**

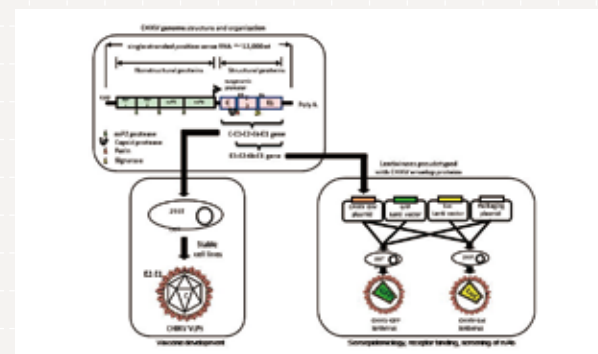
- (1) Neutralization activity of patient sera collected during the 2008-2009 Chikungunya outbreak in Thailand. Kishishita N., et al. *J Clin Microbiol* (2015) 53:184-90.
- (2) Occurrence of hepatitis E virus infection in acute hepatitis in Thailand. Siripanyaphinyo U., et al. *J Med Virol* (2014) 86:1730-5.
- (3) Characterization of chikungunya virus-like particles. Noranate N., et al. *PLoS One* (2014) 9:e108169.

The Section of Viral Infections, in collaboration with the NIH, Department of Medical Sciences, Ministry of Public Health of Thailand, focuses on two emerging and re-emerging viral diseases that are prevalent in Asian countries.

One category of viral diseases under study is viral enteric infectious diseases, among which focus is placed on those caused by norovirus, hepatitis A, and hepatitis E. Norovirus causes food poisoning and is the etiologic agent responsible for acute gastroenteritis via human-to-human transmission. We perform evolutionary analysis based on the genotyping of strains that cause pandemics. In addition, our use of recombinant baculoviruses to investigate expression of norovirus virus-like particles, followed by production of monoclonal antibodies, is ongoing. The ultimate goal is to develop rapid diagnostic tools.

A second category of diseases are mosquito-borne infections, particularly chikungunya fever, which we investigate from an epidemiological, molecular biological, and immunological point of view. We have developed a neutralizing antibody-based assay using a lentivirus pseudotyped with chikungunya virus envelope proteins. A recombinant baculovirus system produces chikungunya virus-like particles, which are used to examine the possibility of

developing a chikungunya vaccine. In addition, analysis of various cell libraries to identify and isolate the cellular factors required for the virus replication is ongoing.



**Fig.** Upon expression, CHIKV (BSL3) structural proteins self-assemble into virus-like particles that are morphologically and antigenically similar to those of native CHIKV. A lentivirus pseudotyped with CHIKV envelope proteins (BSL2) was also used in the CHIKV neutralization test.

**Profile**

Dr. Hamada received D.D.S. and Ph.D. degrees from Osaka university in 1967 and 1971, respectively. He joined the same university as an Assistant Professor from 1977 and an Associate Professor in 1977. He became the Director of Dental Research, National Institute of Health in 1980. He was appointed to current position in 2009 after working as Professor of Microbiology in Osaka University School of Dentistry from 1986 to 2005 and a Professor of Nihon University Advanced Research Institute for the Sciences and Humanities from 2005 to 2009.

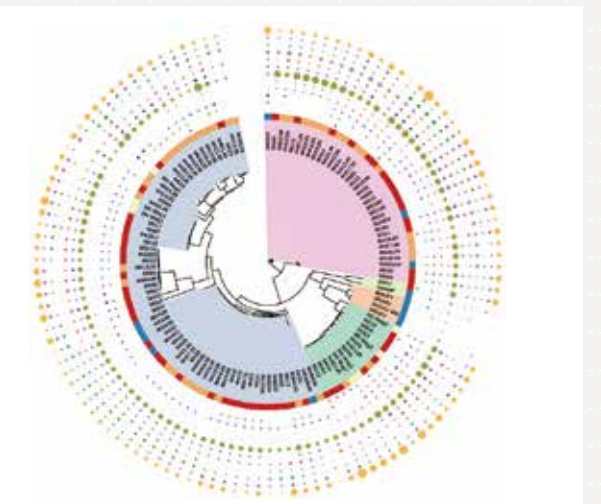
**Publication**

- (1) PCR-Dipstick chromatography for differential detection of carbapenemase genes directly in stool specimens. Shanmugakani, R.K., et al. *Antimicrob Agents Chemother*. 2017 Apr 3. doi:10.1128/AAC.00067-17.
- (2) Fetal septic meningitis in child caused by Streptococcus suis serotype 24. Kerdin, A., et al. *Emerg. Infect. Dis.* (2016) 22(8): 1519-1520.
- (3) Molecular and genomic characterization of pathogenic traits of group A Streptococcus pyogenes. Hamada S., et al. *Proc. Jpn Acad. Sci.* (2015) B91: 539-559.
- (4) Characterization of 3 megabase-sized circular replicons from *Vibrio cholerae*. Okada K., et al. *Emerg. Infect. Dis.* (2015) 21(7): 1262-1263.

SA Professor  
**Shigeyuki Hamada (SUP)**



Carbapenem-resistant Enterobacteriaceae (CRE), including *Klebsiella pneumoniae* and *Escherichia coli*, are highly resistant to carbapenems and many other antibiotics. The rapidly increasing prevalence of CRE over the past decade has increased concern in healthcare facilities and public health communities worldwide. Japan is no exception, even though the prevalence of CRE at this time remains low. Our aim is to examine the epidemiological dissemination of CRE in the Southeast Asian countries. Carbapenem resistance is usually carried by plasmid(s) that harbor genes encoding carbapenemases, i.e., class A KPCs, class B metallo- $\beta$ -lactamases (including IMP, VIM, or NDMs), or class D OXA-type enzymes. We have attempted to isolate CRE from patients admitted to leading hospitals in Thailand and Myanmar. CRE isolates are identified by biochemical characterization or MALDI-TOF-MS, followed by profiling using pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST). We then determine the whole genome sequence of CRE isolates to identify the full plasmid and construct a comprehensive image of the relationships between isolates based on MLST and phylogeny. By undertaking these genomic epidemiological studies, we increase our understanding of how CRE spread and may be able to identify potential reservoirs.



**Figure.** A whole genome SNP-based phylogenetic tree of CRE isolates from Myanmar. The inner colored regions define bacterial species. Next outer colored regions denote the origins of isolates. Colors and sizes of outer dots denote classes and numbers of antimicrobial resistance genes harbored by each isolate.



Prof.  
Tatsuo Shioda (SUP)



Profile

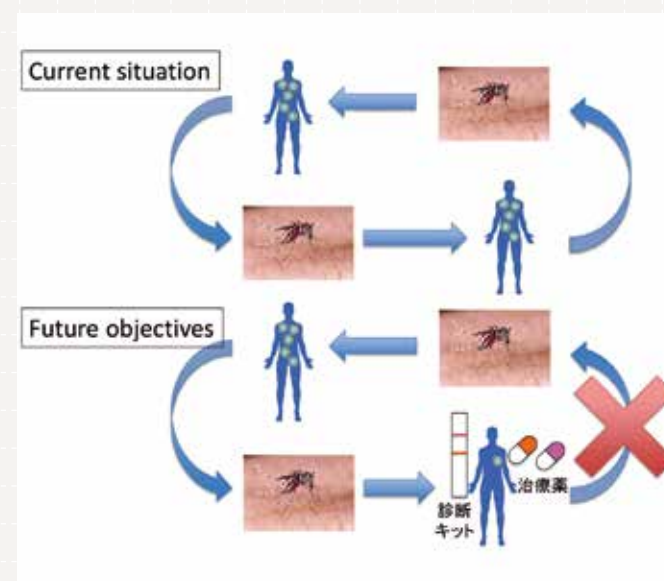
Dr. Shioda obtained his B. Sc. from the University of Tokyo in 1982 and his Ph.D. from the same institution in 1990. After working at the Institute of Medical Science in the University of Tokyo and University of California San Francisco, he was appointed as Associate Professor in 1997. He took his current position as a Professor of RIMD in 2000.

Publication

- (1) Capsid-CPSF6 Interaction Is Dispensable for HIV-1 Replication in Primary Cells but Is Selected during Virus Passage In Vivo. Saito A., *J Virol.* (2016) 11;90 (15):6918-35.
- (2) Roles of Capsid-Interacting Host Factors in Multimodal Inhibition of HIV-1 by PF74. Saito A., *J Virol.* (2016) 27;90 (12):5808-23
- (3) Macaque-tropic human immunodeficiency virus type 1: breaking out of the host restriction factors. Saito A, Akari H. *Front Microbiol.* (2013) 9;4:187.

Recently, climate change and urbanization have increased the risk of vector-borne diseases. Dengue and chikungunya viruses cause dengue fever/hemorrhagic fever and chikungunya fever, respectively. Both viruses are transmitted by *Aedes* mosquitoes. In 2014, there was an outbreak of dengue fever in Tokyo. However, no antiviral drugs are available to treat these infections. Our aim is to develop antiviral drugs against dengue and chikungunya viruses.

Four serotypes of dengue virus are distributed across the world, and re-infection with different serotypes of dengue virus leads to a more severe infection. We aim to develop novel diagnostic tools that can differentiate between the four serotypes of dengue virus.



The Mahidol-Osaka Center for Infectious Diseases (MOCID) focuses on several tropical infectious diseases that are of importance to human health in Thailand. Mosquito-borne viral infectious diseases such as dengue fever/dengue hemorrhagic fever and chikungunya fever are of particular interest. We are currently developing rapid diagnosis kits and are examining factors that affect disease severity. We would like to improve the research skills of young scientists and increase their interest in infectious diseases by collaborating with Mahidol University, which provides clinical samples.

Publication

- (1) Detection of chikungunya virus antigen by a novel rapid immunochromatographic test. Okabayashi T., et al. *Clin Microbiol.* (2015) 53(2):382-8.
- (2) Chikungunya virus was isolated in Thailand, 2010. Sasayama M., et al. *Virus Genes* (2014) 49(3):485-9.
- (3) Monoclonal antibody targeting chikungunya virus envelope 1 protein inhibits virus release. Masrinoul P, et al. *Virology* (2014) 464-465:111-7.
- (4) Low levels of antibody-dependent enhancement in vitro using viruses and plasma from dengue patients. Chaichana P., et al. *PLoS One.* (2014) 18;9(3):e92173.



Diagnostic kit developed by the MOCID.



Evaluation of CHIKV detection kit at Safdarjung Hospital, Delhi, India



Evaluation of CHIKV detection kit at the Institute of Tropical Medicine Antwerp, Belgium





Director, SA Professor  
**Koichi Yamanishi M.D., Ph.D.**

As the recent Ebola virus outbreak in Africa and the world-wide influenza pandemic have powerfully demonstrated, society demands the development, production, and distribution of vaccines against infectious diseases. To meet this strong demand, The Research Foundation for Microbial Diseases of Osaka University (BIKEN) and the Research Institute for Microbial Disease, Osaka University (RIMD), have established a new research organization, called The BIKEN Innovative Vaccine Research Alliance Laboratories, to promote the co-operative development of vaccines. Here, we are developing new technologies to acquire basic information required to design next-generation vaccines.



**A regular meeting between laboratories.**

All members for this research project attend the meeting. Researchers address their research topics in depth and take part in active discussions.



**Experimental laboratories.**

Researchers can move freely among three laboratories. All three laboratories have common equipment.

Postdoc. : Hideki Takahashi /  
Postdoc. : Kazuki Misato /  
Undergrad. Student 4 /  
Grad. Student 1

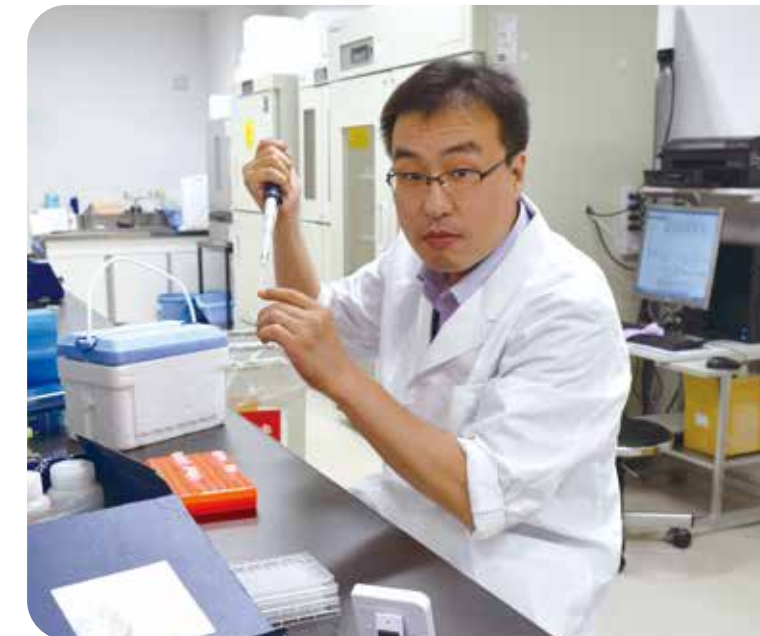
## Profile

Dr. Yoshioka received his Ph.D. from Osaka University in 2004. He took his current position at RIMD from 2015 after working at National Institute of Health Sciences, the Center for Advanced Medical Engineering and Informatics and Grad. School of Pharmaceutical Sciences in Osaka University.

## Publication

- (1) Distribution of silver nanoparticles to breast milk and their biological effects on breast-fed offspring mice. Morishita Y, Yoshioka Y, et al. *ACS Nano*. (2016) Aug 15.
- (2) Metal nanoparticles in the presence of lipopolysaccharides trigger the onset of metal allergy in mice. Hirai T, Yoshioka Y, et al. *Nat Nanotechnol*. (2016) 11 (9):808-16.
- (3) Silica and titanium dioxide nanoparticles cause pregnancy complications in mice. Yamashita K, Yoshioka Y, et al. *Nat Nanotechnol*. (2011) 6(5):321-8.
- (4) Interleukin-1 family cytokines as mucosal vaccine adjuvants for induction of protective immunity against influenza virus. Kayamuro H, Yoshioka Y, et al. *J Virol*. (2010) 84(24):12703-12.

## SA Associate Professor Yasuo Yoshioka



Most protein antigens such as non-living macromolecules or protein-subunit antigens evoke weak or undetectable adaptive immune responses. Therefore, to develop effective vaccines it is necessary to develop vaccine adjuvants and antigen delivery carriers. In addition, to develop optimal (in terms of efficacy and safety) vaccines for clinical application, it is important to understand the mechanism by which vaccines act on the immune system. In this regard, our research is focused on optimizing vaccines through drug delivery systems and safety science. Our specific research projects are:

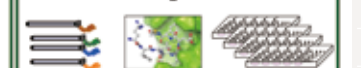
- 1) Development of vaccine adjuvants using comprehensive screening methods.
- 2) Development of antigen delivery carriers and adjuvants using nanotechnology.
- 3) To use these adjuvants and delivery carriers to develop vaccines for infectious diseases.

**Our research is focused on optimizing vaccines related to drug delivery systems and safety science.**

Development of antigen delivery carriers and adjuvants using nanotechnology



Development of vaccine adjuvant using comprehensive screening methods



**Development of vaccines for infectious diseases using our developed adjuvants and delivery carriers**



SA Associate Professor  
**Shintaro Sato**



**Profile**

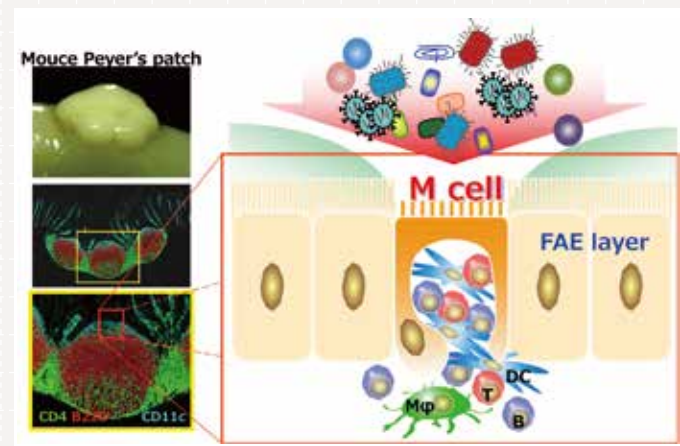
Dr. Sato received his master's degree from Hokkaido university in 1999 and his Ph.D. from Osaka University in 2003. He took his current position in 2015 after working at RIMD as a Postdoctoral fellow and at University of Tokyo as an Assistant Professor.

**Publication**

- (1) Allograft inflammatory factor 1 is a regulator of transcytosis in M cells. Kishikawa S., et al. *Nat. Commun.* (2017) 8:14509.
- (2) IL-10-producing CD4<sup>+</sup> T cells negatively regulate fucosylation of epithelial cells in the gut. Goto Y., et al. *Sci. Rep.* (2015) 5:15918.
- (3) Innate lymphoid cells regulate intestinal epithelial cell glycosylation. Goto Y., et al. *Science* (2014) 345 (6202):1254009.
- (4) Transcription factor Spi-B-dependent and -independent pathways for the development of Peyer's patch M cells. Sato S., et al. *Mucosal Immunol.* (2013) 6(4):838-46.

Because most pathogens invade and infect their host via mucosal tissues, mammals have established a strictly organized and dynamic immune system at mucosal surfaces. This system, named the mucosal immune system, combats infectious pathogens. The development of mucosal vaccines, which activate mucosal and systemic immune responses, is receiving increasing attention. We have focused on epithelial cells, particularly M cells, which are professional antigen uptake cells located in areas that come into contact with non-self-antigens. Our main research themes are:

- 1) To identify new M cell-specific genes and elucidate the mechanism of M cell antigen uptake.
- 2) To understand the aged mucosal immune system and develop effective mucosal vaccines for older people.
- 3) To establish an *in vitro* culture system for normal and functional primary mucosal epithelial cells and use it to screen for candidate mucosal vaccine antigens and adjuvants.



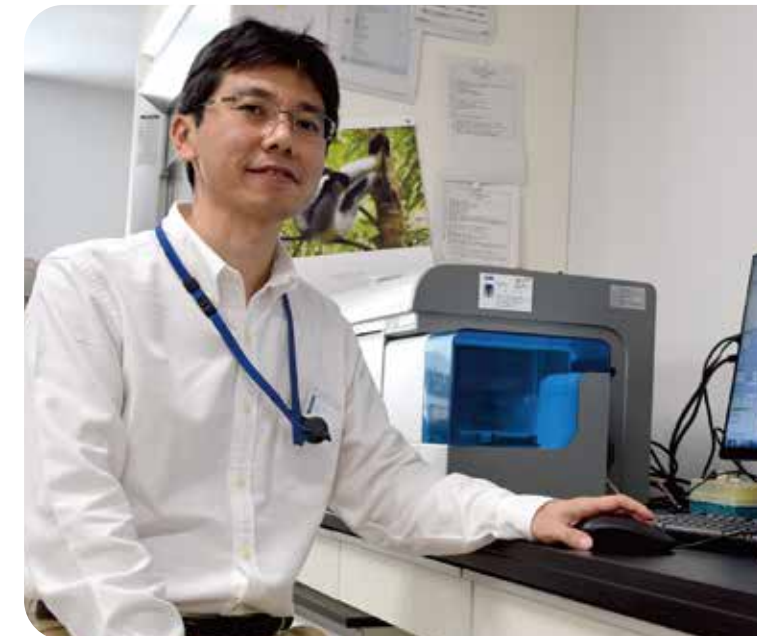
**Profile**

Dr. Aoshi received his M.D. from Hamamatsu University School of Medicine in 1999 and his Ph.D. from the same institution in 2006. He was appointed current position in 2015 after working at Washington University in St. Louis, NIBIOHN, and IFRc in Osaka University.

**Publication**

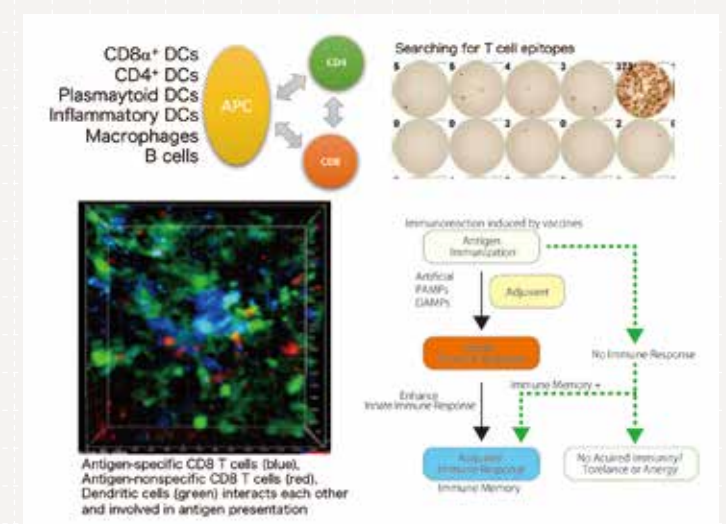
- (1) Development of non-aggregating poly-A tailed immunostimulatory A/D-type CpG oligodeoxynucleotides applicable for clinical use. Aoshi T., et al. *J Immunol Res.* (2015) 2015:316364. doi: 10.1155/2015/316364.
- (2) Plasmacytoid dendritic cells delineate immunogenicity of influenza vaccine subtypes. Koyama S., et al. *Sci Transl Med.* (2010) Mar 31; 2(25):25ra24.
- (3) The cellular niche of *Listeria monocytogenes* infection changes rapidly in the spleen. Aoshi T., et al. *Eur J Immunol.* (2009) Feb; 39(2):417-25.
- (4) Bacterial entry to the splenic white pulp initiates antigen presentation to CD8<sup>+</sup> T cells. Aoshi T., et al. *Immunity* (2008) Sep 19; 29(3):476-86.

SA Associate Professor  
**Taiki Aoshi**



Vaccination, which utilizes the built-in "immune system" in the body, is one of the most successful medicine for controlling microbial infections. The immune system comprises many different immune cells. T cells are one of the most important immune cells that help to establish protective immunity against many pathogens. In addition, T cells are also involved in many non-infectious conditions such as autoimmunity and cancer.

Although T cells are critically involved in many diseases, current vaccines (with the exception of attenuated live vaccines) cannot induce sufficiently strong T cell responses. We are developing "T cell inducing vaccine" through the studies of T cell epitope and T cell/antigen presenting cell interaction. We are also developing clinically applicable "nucleic acid adjuvants" that not only induce strong Th1/CTL responses but also retain good safety profiles. We believe that the understanding of T cell epitope, T cell/antigen presenting cell interactions, and the development of new adjuvants will enable us to make safer and more effective T cell inducing vaccines in the near future.





## Animal Resource Center for Infectious Diseases

### Staff

Head, Prof. (SUP) : Masahito Ikawa, Ph.D.  
 Assoc. Prof. : Yuhkoh Satouh, Ph.D.  
 Asst. Prof. (SUP) : Yoshitaka Fujihara, Ph.D.  
 Asst. Prof. (SUP) : Haruhiko Miyata, Ph.D.  
 Asst. Prof.(SUP) : Taichi Noda, Ph.D.  
 SA Asst. Prof. (SUP) : Daiji Kiyozumi, Ph.D.

To study infectious diseases and cancer, it is important to analyze interactions between pathogenic factors and the human body. Animal models are indispensable for biomedical research, particularly since molecular biology and biotechnology methods can be used to generate genetically modified mice that aid our understanding of the molecular mechanisms underlying such diseases. Experimentally infected animals and genetically engineered animals used for these purposes should be managed in a suitable, safe, and controlled manner. The Animal Resource Center for Infectious Diseases is a unique facility that was established in 1967 to meet these requirements.

The center is equipped with pass-through-type autoclave systems and HEPA filtered air exchange systems to minimize the risk of contamination so that infected or genetically engineered animals are maintained in a safe environment. The animals are housed in three areas: SPF (specific pathogen free), BSL (biosafety level) 2, and BSL3. Before gaining access to restricted areas, researchers must take an official orientation and submit a research plan for committee review. The condition of the animals is monitored regularly.

Our facility provides the following services: generation of genetically manipulated animals, *in vitro* fertilization, and cryopreservation of mouse strains (Table 1). The facility provides these services in co-operation with the Department of Experimental Genome Research.

|           | IVF/ET | TG  | KO, KI |
|-----------|--------|-----|--------|
| -2000     | 261    | 228 | 50     |
| 2001-2003 | 443    | 104 | 57     |
| 2004-2006 | 331    | 43  | 69     |
| 2007-2009 | 216    | 22  | 74     |
| 2010-2012 | 388    | 55  | 152    |
| 2013-2015 | 580    | 50  | 242*   |

**Table 1** \*Tg, Transgenic; KO, Knockout; IVF, *in vitro* Fertilization; ET, Embryo transfer.

\* Includes lines generated using the CRISPR/Cas9 genome editing system.



#### Biosafety level 3 room.

The room is used for research involving disease model animals at biosafety level 3. Hemorrhagic fever with renal syndrome-causing virus (HFRSV) was isolated in this area. In addition, animal experiments involving Zika virus, SARS, and Acquired Immune Deficiency Syndrome (AIDS), can be handled in this facility.



#### Buildings at the Animal Resource Center.

Building A (in front of the chimney, built in 1967, two-story).  
 Building B (rear right of the chimney, built in 1978, four-story).  
 Building C (on the right side of Building A, built in 2009, four-story).

## Office of Combined Program on Microbiology and Immunology

Our institute and the Immunology Frontier Research Center are world-class institutes for microbiological and immunological research, respectively. To take maximal advantage of this situation and to foster intellectual exchange between these two institutes, we have developed a combined microbiology and immunology program.

To facilitate research on microbiology and immunology, we organize following programs. The aim of these activities is to promote communication between researchers and to develop human resources with expertise covering both microbiology and immunology.

1. **Awaji International Forum on Infection and Immunity (annually in September).** <http://awaji-forum.com>
2. **The Biken monthly seminar for reporting research progress.**
3. **The Annual Research presentation program and the competition of research presentations.**
4. **Lecture Programs for Graduate Students.**
5. **Orientation and Lab Tour for RIMD and IFRc for candidates of graduate schools/post doctoral positions.**



Associate Professor :  
 Ryo Iwamoto,  
 Ph.D.



Awaji International Forum



A seminar held in December



Academic Prize awardee



Awaji Yumebutai  
 International Conference Center



Lecture series for graduate students



Joint Orientation for RIMD and IFRc

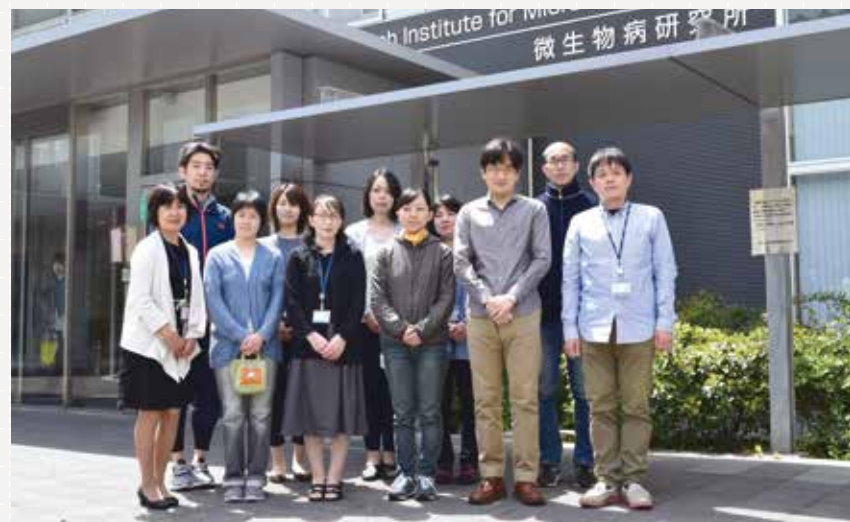


## Common Research Facilities

### Central Instrumentation Laboratory

Head, Professor (SUP) :  
**Hiroaki Miki, Ph.D.**  
Associate professor:  
**Shinji Higashiyama, Ph.D.**  
Associate professor:  
**Naohisa Goto, Ph.D.**

The Central Instrumentation Laboratory was established in 1959. When equipment was lacking in many laboratories, researchers brought their machines together and co-operated with each other. Now, various pieces of precision apparatus and high performance machines are available in the laboratory at all times. These include ultracentrifuges, transmission and scanning electron microscopes, a Biacore system, cell analyzer/sorters, an DNA sequencers, and mass spectrometers. Also, large cell storage tanks equipped with automatic liquid nitrogen supply systems and a specified chemical treatment room are also present. In addition, professional technicians are employed to maintain and manage these devices, as well as to provide services, education, and training for newcomers. They also provide in-house services such as cell sorting, mass spectrometry-based protein identification, electron microscope image capture, and DNA sequencing. As experimental machines become more and more complicated, the services provided by specialist staff are essential for ongoing research at the institute.



Central Instrumentation Laboratory



Central Laboratory for Biological Hazardous Microbes

This BSL-3 laboratory was set up in 1983 to ensure the safe handling of biologically hazardous microbes such as hemorrhagic fever with renal syndrome (HFRS) virus. All experimental studies using hazardous microbes, such as HIV, should be handled in this laboratory. The laboratory is a three-story building with 550 m<sup>2</sup> of floor space. The facilities are designed to protect researchers from pathogenic infection and to prevent the spread of biohazardous pathogens outside the building. The supply of fresh air is regulated to keep the room interiors at negative pressure. High-quality filters are installed on the exhaust outlet to minimize microbial contamination of the environment. Each room is equipped with safety cabinets and autoclaves to sterilize used material before disposal. Researchers must be approved by the Biosafety Committee before they use this laboratory. Various microbes, including HIV, SARS corona virus, and scrapie agent, are studies in this facility.

General Affairs Section  
Accounting Section  
Research Cooperation Section  
Planning Office  
PR Office

## Common Research Facilities

### Central Laboratory for Biological Hazardous Microbes

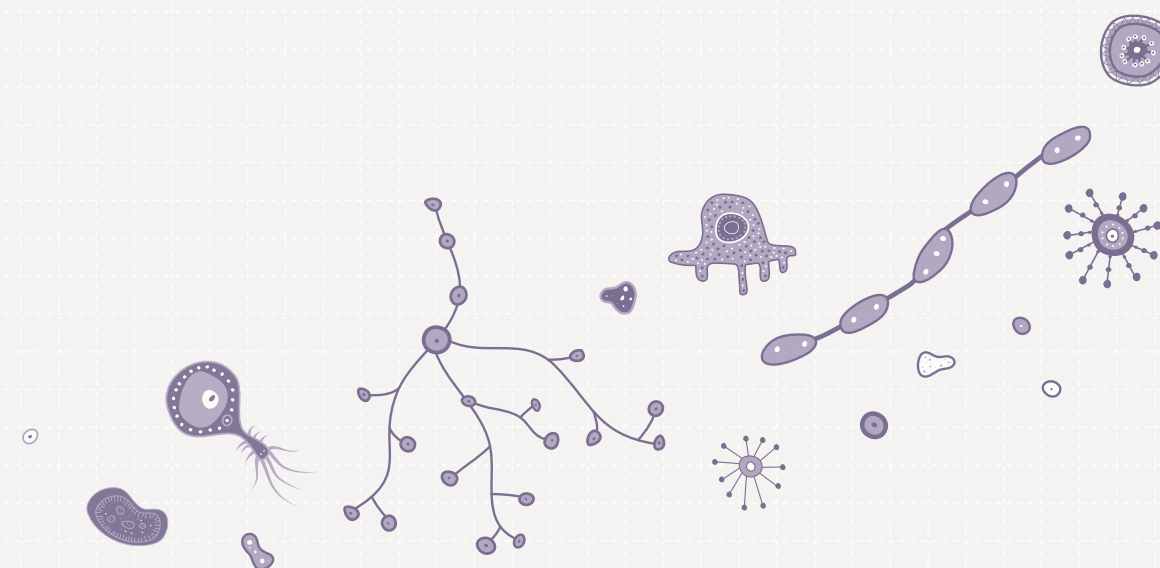
Head, Professor (SUP) :  
**Tatsuo Shioda, Ph.D.**

### Administration and Research Support

### Radioisotope Laboratory

Head, Professor (SUP) :  
**Hiroaki Miki, Ph.D.**

The radioisotope (RI) laboratory was established in 1967 and was designed for biomedical experiments involving RIs. Now, RIMD researchers perform RI experiments in the RI Laboratory at the Immunology Frontier Research Center at 9F, the Central Laboratory for Biological Hazardous Microbes at 1F, and the radiation exposure room in the North building at 1F. Facilities include a RI stock-room, a distribution room, a tissue culture room, and an area for RI measuring equipment. Safety requirements are met by a stringent security system that involves the use of ID cards and the computerized management of RIs.





## RIMD History

The Research Institute for Microbial Diseases (RIMD) was established in 1934 to study microbial and infectious diseases, the immune system, and cancer. The RIMD of today is the result of the hard work and amazing achievements of many researchers over the years.

### Research Institute for Microbial Diseases opened

RIMD was founded through a merger of the Research Center for Communicable Diseases (Osaka Medical School), the Takeo Tuberculosis Institute (donated by Mr. Jiemon Takeo), and the Osaka Leprosy Institute (donated by an anonymous benefactor).



1930

1940

1950

1960

1967

1970

1980

1990

2000

2010

Discovered  
*Vibrio  
parahaemolyticus*  
Tsunesaburo Fujino

Discovered  
cell fusion  
Yoshio Okada

Developed  
a measles  
vaccine  
Yoshiomi Okuno

Discovered  
a viral  
oncogene  
Kumao Toyoshima

Developed  
a chickenpox  
vaccine  
Michiaki Takahashi

Elucidation  
of the Innate  
Immune System  
Shizuo Akira

Approved as a Joint  
Usage/Research  
Center by  
MEXT

Developed  
a malaria  
vaccine  
Toshihiro Horii

### Institute construction was completed

With financial support from Gendo Yamaguchi, a benefactor from Osaka, the RIMD main building was constructed in Dojima, Osaka.

Tenji Taniguchi

Professor of Bacteriology at the Osaka Medical school. He played a huge role in the foundation of RIMD as he emphasized the need for a research institute in the KANSAI area that focused on microbial or infectious diseases.



Prof. Taniguchi (right) and Lab Members

Gendo Yamaguhi

A successful businessman in the KANSAI area. He gave back to the community by offering his property for public benefit services and temples. He donated 200,000 yen to establish RIMD.



## Biken History Museum



The Biken History Museum opened in 2010. Many precious items related to RIMD are on display. People both inside and outside Osaka University can visit the museum.



Koch's microscope

Opening hours: 9:00–17:00 (Mon–Fri)  
Location: RIMD Main Building 1F  
Fee: Free

Biken History Museum website  
<http://museum.biken.osaka-u.ac.jp/english/home.html>



The first ultracentrifuge rotor, installed about 60 years ago



A manipulator used for research in RIMD



A model of the HEV-hepatitis E virus



Prof. Tenji Taniguchi's Desk

Pictures and materials are provided by Biken History Museum



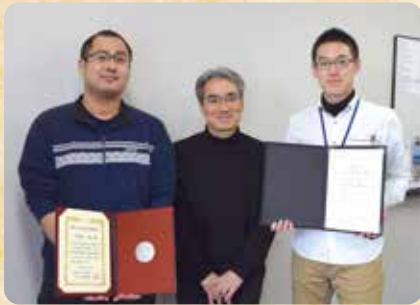
RIMD Awards 2016-17



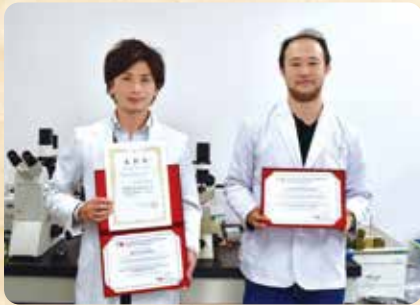
|                                                                                                                                                                      |                                                                                      |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------|
| Best Article Award, Experimental Animals,<br>The 63rd Annual Meeting of Japanese Association for Laboratory Animal Science                                           |                                                                                      |            |
| Masahito Ikawa                                                                                                                                                       | Dept. of Experimental Genome Research Animal Resource Center for Infectious Diseases | 2016.5.19  |
| Incentive Award, The Japanese Society for Epigenetics 2016                                                                                                           |                                                                                      |            |
| Toshitsugu Fujita                                                                                                                                                    | Chromatin Biochemistry Research Group                                                | 2016.5.20  |
| Incentive Award, The 8th Signal Network Workshop                                                                                                                     |                                                                                      |            |
| Hiroya Okura                                                                                                                                                         | Dept. of Oncogene Research                                                           | 2016.5.27  |
| Best Presentation Award, The 37th Annual Meeting of the Japanese Society of Inflammation and Regeneration                                                            |                                                                                      |            |
| Jia Weizhen                                                                                                                                                          | Dept. of Signal Transduction                                                         | 2016.6.17  |
| Best Presentation Award, Workshop for Young Scientists 2016,<br>Establishing a new paradigm of pathogenesis of diseases through the understanding of stem cell aging |                                                                                      |            |
| Taichi Noda                                                                                                                                                          | Dept. of Experimental Genome Research                                                | 2016.7.29  |
| The 7th Incentive Award for Young scientists, Section for Veterinary Microbiology,<br>The Japanese Society of Veterinary Science                                     |                                                                                      |            |
| Keisuke Ishigaki                                                                                                                                                     | Dept. of Molecular Bacteriology                                                      | 2016.9.8   |
| Best Presentation Award, The 4th Young Researchers Forum on Infectious Diseases                                                                                      |                                                                                      |            |
| Naoaki Shinzawa                                                                                                                                                      | Dept. of Molecular Bacteriology                                                      | 2016.9.8   |
| Oral Presentaion Award, The 109th Annual Meeting for the Society for Reproduction and Development                                                                    |                                                                                      |            |
| Taichi Noda                                                                                                                                                          | Dept. of Experimental Genome Research                                                | 2016.9.14  |
| CALAS International Award for Young Scientists,<br>The 12th Scientific Conference of Chinese Association for Laboratory Animal Sciences                              |                                                                                      |            |
| Haruhiko Miyata                                                                                                                                                      | Dept. of Experimental Genome Research                                                | 2016.10.11 |



Keisuke Ishigaki (right),  
Dept of Molecular Bacteriology



Toru Okamoto (left) and  
Kentaro Uemura (right),  
Dept of Molecular Virology



Hiroyasu Kidoya (left) and  
Fumitaka Muramatsu (right),  
Dept of Signal Transduction

|                                                                                                                 |                                 |            |
|-----------------------------------------------------------------------------------------------------------------|---------------------------------|------------|
| IWAA2016 Award                                                                                                  |                                 |            |
| Kenji Tanimura                                                                                                  | Dept. of Immunochemistry        | 2016.10.13 |
| IWAA2016 Award                                                                                                  |                                 |            |
| Ryosuke Hiwa                                                                                                    | Dept. of Immunochemistry        | 2016.10.13 |
| Sugiura Incentive Award, The 64th Annual Meeting of the Japanese Society for Virology                           |                                 |            |
| Toru Okamoto                                                                                                    | Dept. of Molecular Virology     | 2016.10.23 |
| Best Poster Award, The 64th Annual Meeting of the Japanese Sociy for Virology                                   |                                 |            |
| Kentaro Uemura                                                                                                  | Dept. of Molecular Virology     | 2016.10.25 |
| JVBMO2016 Travel Award, The 19th International Vascular Biology Meeting                                         |                                 |            |
| Hiroyasu Kidoya                                                                                                 | Dept. of Signal Transduction    | 2016.10.30 |
| JVBMO2016 Travel Award, The 19th International Vascular Biology Meeting                                         |                                 |            |
| Fumitaka Muramatsu                                                                                              | Dept. of Signal Transduction    | 2016.10.30 |
| Poster Presentation Award,<br>The 48th Annual Meeting of the Japanese Society for Pediatric Infectious Diseases |                                 |            |
| Koichiro Suzuki                                                                                                 | Dept. of Molecular Bacteriology | 2016.11.20 |
| Oral Presentation Award, The 61st congress of the Japanese Society of Oral and Maxillofacial Surgeons           |                                 |            |
| Emi Fujibayashi                                                                                                 | Dept. of Molecular Genetics     | 2016.11.26 |
| Early Carrier Investigator Award, The 11th International Symposium of The Institute Newwork                     |                                 |            |
| Hiroyasu Kidoya                                                                                                 | Dept. of Signal Transduction    | 2017.1.27  |
| Best Presentation Award 2016, The 45th Annual Meeting of the Japanese Society for Immunology                    |                                 |            |
| Kouyuki Hirayasu                                                                                                | Dept. of Immunochemistry        | 2017.2.8   |

Highly cited researchers 2016

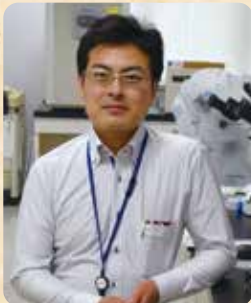
2016.11.17



Shizuo Akira  
Department of  
Host Defense



Masahiro Yamamoto  
Department of  
Immunoparasitology



Shintaro Sato  
Mucosal Vaccine Project



## RIMD Joint Usage / Research Center

RIMD was certified as a “Joint Usage/Research Center” by the Ministry of Education, Culture, Sports, Science and Technology in Japan (MEXT) in 2010. The “Joint Usage/Research Center” is a sharing system first organized by MEXT in 2008 and which allows Japanese researchers to use facilities, equipment, and databases at inter-university research institutes.

The aims of RIMD as “Joint Usage/Research Center” are to promote research and develop human resources in the fields of immunology, bacteriology, and oncology.

### Research projects

|       | General Research project,<br>Short term | Specific Research project,<br>Short term | Research project,<br>Long term | To help victims of<br>the earthquake | Total |
|-------|-----------------------------------------|------------------------------------------|--------------------------------|--------------------------------------|-------|
| 2010  | 18                                      | 4                                        | 8                              |                                      | 30    |
| 2011  | 16                                      | 3                                        | 7                              | 2                                    | 28    |
| 2012  | 22                                      | 4                                        | 6                              | 2                                    | 34    |
| 2013  | 18                                      | 10                                       | 11                             |                                      | 39    |
| 2014  | 18                                      | 11                                       | 11                             |                                      | 40    |
| 2015  | 17                                      | 12                                       | 9                              |                                      | 38    |
| 2016  | 18                                      | 11                                       | 5                              |                                      | 34    |
| 2017  | 12                                      | 15                                       |                                |                                      | 27    |
| Total | 139                                     | 70                                       | 57                             | 4                                    | 270   |

**General Research Project** Researches for host defense and pathogens, basic biological research

**Specific Research Project** Researches for infectious diseases and pathogens

※ Short term project: 1 year, Long term project: 3 year

### International Collaboration

RIMD researchers conduct international collaborative projects that involve participation of researchers overseas. RIMD also concludes academic agreements with four universities in Africa and Asia.

### International collaborative projects

| Year     | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|----------|------|------|------|------|------|------|
| Projects | 24   | 42   | 49   | 42   | 32   | 35   |

### Academic agreements

| Country            | Institute / University                           |
|--------------------|--------------------------------------------------|
| Republic of Uganda | Faculty of Medicine, Gulu University             |
| Thailand           | Bamrasnaradura Infectious Diseases Institute     |
| Thailand           | Faculty of Tropical Medicine, Mahidol University |
| Indonesia          | Faculty of Medicine, Airlangga University        |

### Seminars and Symposia

RIMD hosts international symposiums to share research achievements and facilitate communication among researchers.

#### ● Seminars

##### Advanced Seminar Series on Microbiology and Immunology

Lecture series hosted by RIMD. Leading researchers in the field of Microbiology and Immunology are invited to this lecture series.

##### Bridge seminar

Seminar series hosted by young researchers in RIMD.



### International Symposia

| Symposiums                                                                                                                                 | Date         | Participants |
|--------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|
| Awaji International Forum on<br>Infection and Immunity  | 2016/9/5-8   | 211          |
|                                                                                                                                            | 2015/9/8-11  | 183          |
|                                                                                                                                            | 2014/9/23-26 | 203          |
|                                                                                                                                            | 2013/9/10-13 | 195          |
|                                                                                                                                            | 2012/9/11-14 | 215          |
|                                                                                                                                            | 2010/9/7-10  | 240          |
|                                                                                                                                            | 2009/9/8-11  | 252          |
| France-Japan International Exchange Symposium                                                                                              | 2012/2/10    | 52           |
|                                                                                                                                            | 2010/2/4     | 20           |
| RIMD-CVRDC Joint Symposium                                                                                                                 | 2012/5/10-12 | 71           |
|                                                                                                                                            | 2010/6/17-18 | 61           |
| International Symposium of the Institute Network※                                                                                          | 2014/6/19-20 | 158          |

※Joint hosting with Institute for Protein Research, Osaka University



**RIMD**  
Joint Usage/  
Research Center

Triangle  
Relationships  
on Infectious Diseases  
and Immunology



WPI Osaka University  
**iFReC**

World Premier  
International Research Center  
on immunology



**BIKEN**

Translation of Research findings by RIMD  
and IFReC into practical social applications,  
such as vaccine production

RIMD and IFReC conducts world-class researches in biological fields including the fields of microbiology and immunology. RIMD and IFReC collaborate each other to promote researches and foster talented human resources in these fields.

The BIKEN foundation develops vaccines, thereby to translate the research achievements in of RIMD and IFReC to the whole of society. In addition, the foundation is dedicated to promoting basic research by through the Taniguchi Memorial Scholarship program and the BIKEN Center for Innovative Vaccine Research Alliance Laboratories.



## For Students and Researchers who wants to study in RIMD



RIMD is one of the world's foremost institute in immunology, microbiology and cancer research. We also conduct research in various bioscience related fields including gene engineering, genomic science and bioinformatics. We welcome motivated grad-students and researchers from around the world.

The way to join RIMD would be different depends on the situation. Candidate for grad-school students or post-docs may need to decide the lab to join and then ask PIs how to belong to RIMD.

The Orientation and lab tour would be held in May every year. Please check our website for detail.

[http://suishin.biken.osaka-u.ac.jp/setsumeikai/setsumeikai\\_en.html](http://suishin.biken.osaka-u.ac.jp/setsumeikai/setsumeikai_en.html)

### Information in Osaka University website

#### > Osaka University website for Global Affairs

<http://www.osaka-u.ac.jp/en/international>



#### > Osaka University website for International Students

<http://www.osaka-u.ac.jp/en/for-student>



#### > Osaka University Support Office for international Students

<https://iss-intl.osaka-u.ac.jp/supportoffice/>



#### > Osaka University International Students Association

<http://ouisa.info/>



#### > Osaka University Brothers and Sisters Program (BSP)

An International-exchange circle organized by Osaka University Students to support international students.

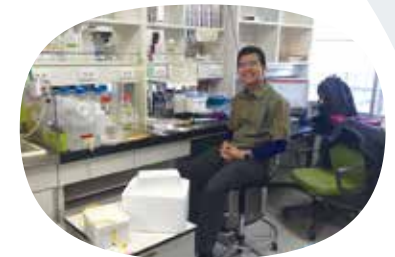
<http://www.bsp-ou.net/>



#### > Osaka University COOP guidance book

The Osaka University COOP is a non-profitable organization for students and staffs in Osaka university. They provide stores, cafeterias and other life supports including housing and traveling.

<http://www.osaka-univ.coop/english/index.html>



### Information in Japanese Government or Organization

#### > Study in Japan Comprehensive Guide by The Ministry of Foreign Affairs of Japan

<http://www.studyjapan.go.jp/en/index.html>



#### > Websites of Japanese Embassies in your country

[http://www.mofa.go.jp/about/emb\\_cons/mofaserv.html](http://www.mofa.go.jp/about/emb_cons/mofaserv.html)



#### > Japan Student Services Organization (JASSO)

An independent administrative institution established under the MEXT, comprehensively administers support programs for international students including scholarship loan programs.

<http://www.jasso.go.jp/en/index.html>



#### > Gateway to study in Japan by JASSO

Information in Japanese, English, Chinese, Korean, Indonesia, Thai, Vietnamese

<http://www.g-studyinJapan.jasso.go.jp>



#### > Japanese Government scholarship by MEXT

<http://www.studyjapan.go.jp/en/toj/toj0302e.html>



#### > Suita International Friendship Association

A public interest Incorporated Foundation to support citizen's international exchange activities and provide assistance to foreigners living or Studying in Suita city.

<http://suita-sifa.org/en/>



RIMD and IFReC conducts world-class researches in biological fields including the fields of microbiology and immunology. RIMD and IFReC collaborate each other to promote researches and foster talented human resources in these fields.

The BIKEN foundation develops vaccines, thereby to translate the research achievements in of RIMD and IFReC to the whole of society. In addition, the foundation is dedicated to promote basic research by through the Taniguchi Memorial Scholarship program and the BIKEN Center for Innovative Vaccine Research Alliance Laboratories.





# Grad Students Studying in RIMD

## Why RIMD?

I have deep interest in learning Japanese language and experiencing the cultures in Japan. Most importantly, the thought of involving in a Japanese research team lead by top university's department is tremendously exciting as it offers me the opportunity to grasp more insight into biological science field, which I particularly admire and appreciate. Thus, I applied for Japanese Government Scholarship (MEXT scholarship), and it took me almost a year to get through the selection process, with a bit of luck I managed to secure the scholarship\*. Since I am interested in the field of oncology, I searched for cancer research labs in Japan and came into contact with Professor Okada Professor Associate Nada via Okada-lab webpage. Both professors were very friendly in guiding and handling my admission in Department of Oncogene, RIMD, Osaka University. Since then, I was admitted as a Research Student in October 2015 and few months later I passed the entrance examination in 2016, I became a graduate student for the Graduate school of Science, Osaka University.

## A day in the life

I am taking Special Integrate Science course in the Graduate school of Science. The course is mainly for international students in which the lectures are held in English. Since some Japanese students are also taking some lectures in SISC program, from the interactive conversation with the local students, we can share and develop deeper understanding in this extraordinary biological world. Apart from that, Sensei and laboratory comrades in the Okada-lab are very friendly. And I wholeheartedly agree to my friends saying that KANSAI people are friendlier than people from east part of Japan. Currently, I really enjoy my daily life in Osaka.

## Research Interest

Coming to graduate school, I knew I wanted to study the basic processes governing cell function and development in a genetically traceable organism. I also wanted to work under the guidance of an advisor who took a primary interest in my scientific work. Therefore, my research is mainly focused on elucidating and comparing the regulation of TGF-B signaling pathway that confers to cancer resistance in Naked Mole Rat (NMR) and house mouse. In brief, NMR is an organism of interest that provides a platform for understanding how cancer resistance can be achieved in mammals in general since it possess exceptional longevity and is remarkably cancer-resistant. Thus, increased insight into molecular mechanism at the interface of aging and age-related disease, such as cancer, is crucial for making progress in improving human health. In a nutshell, it is pivotal to elucidate the signaling pathway of TGF-B in which NMR might rely on this pathway to confer cancer resistance, as compared to its short-lived cancer-prone mice that lack the mechanism that lead to extreme longevity and cancer resistance.

## Message for young students.

I hope that young students will set directions of their own goal, as the direction of one's goal is the direction of one's life will move on. Most importantly, let yourself move towards what is good, valuable, strong and true. And not to forget to try new things and experience enticing adventures, keep moving forward as curiosity surely will lead you down new path and from there you can embark your amazing journey of life.

\*Only 24 students out of several thousand applicants in Malaysia could get the scholarship!

### Woei-Yaw Chee

Department of Oncogene Research (Okada Lab)

Masters course in Graduate school of Science, Osaka university  
BA: National University of Malaysia / Bournemouth university, UK

## Why RIMD?

I approached one of my professors in the East Asian Language and Culture department at UC Berkeley about my future during my last year of college. He insisted that I would be a top candidate for the MEXT scholarship to pursue my Master's degree in Japan given my dual degrees in Biology and Japanese. I have always been passionate about women's health and reproductive biology, so I reached out to one of my biology professors to ask if she had any contacts in Japan. She gave me RIMD Professor Masaru Okabe's email address and I sent him a message about my interest. He quickly replied back saying that while he retired, Professor Ikawa took over the laboratory and to contact him. From there, it all fell perfectly into place. Professor Ikawa was incredibly kind and helpful throughout this journey. I was delighted to learn that the Ikawa lab at Osaka University, one of the top reproductive biology labs in the field, offered the ideal opportunity for me to gain experience and pursue my career aspirations as a researcher focused on the female reproductive system. After securing the MEXT scholarship with his help, I was admitted as a Research Student in April 2015, passed the Master's course entrance exam in August 2015, and became a graduate student in the Graduate School of Medicine at Osaka University.

## A day in the life

The Graduate School of Medicine Master's course is special in that all of the lectures are packed into the first two and a half months of the program. Because the course is mainly for Japanese students, all of the lectures are conducted in Japanese. While it has been a challenge for me to learn biological Japanese vocabulary in the beginning, I can confidently say that my vocabulary has increased tremendously. Not only that, sharing that experience with my Japanese classmates was an amazing opportunity to further develop my Japanese. Now that classes have ended, I am back full time in the Ikawa lab. While continuing to do experiments and furthering the bonds I have with my labmembers, I am also teaching them English and learning to speak the Kansai dialect!

## Research Interest

My family history of reproductive diseases initially motivated me to pursue a scientific career focused on the female reproductive system. As I learned about the health benefits of female contraception specific to ovarian cancer prevention, I became further intrigued with female fertility factors. As a Master's student in Professor Ikawa's lab, I am currently using the CRISPR/Cas9 system to create knockout mice to find genes essential for female fertility. CRISPR/Cas9 is currently the leading technology for gene manipulation. By injecting a signal guide RNA sequence into fertilized mouse eggs, we can recruit the Cas9 protein to cut our target DNA sequence, rendering the protein functionally useless. While the majority of research conducted in this lab is based on the male reproductive system, my passion for the female system urges me to uncover the unknown in female reproduction. For the next two years, my goal as a Master's course student is to find specific female infertility factors that could ultimately be translated into contraception.

## Message for young students.

While I have been studying Japanese since high school, it did not prevent the ups and downs of living in a brand new country. Nonetheless, perseverance, believing in myself, and not being afraid to ask for help has led me to where I am. I am always aware of my privilege and am thankful to those who have supported me. If it were not for my undergraduate professors, I would not be in Japan right now. Finding strong mentors is key to future success.

### Ferheen Abbasi

Department of Experimental Genome Research (Ikawa Lab)

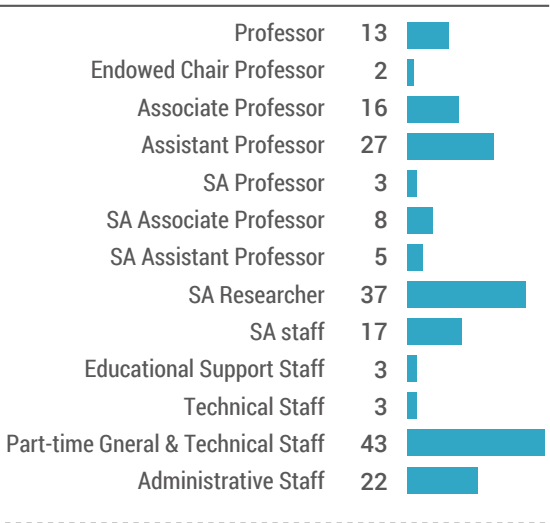
Master's Course in the Graduate School of Medicine  
BA in Molecular and Cell Biology and  
BA in Japanese Language  
from the University of California,  
Berkeley Class of 2014





RIMD STAFF (2017.4)

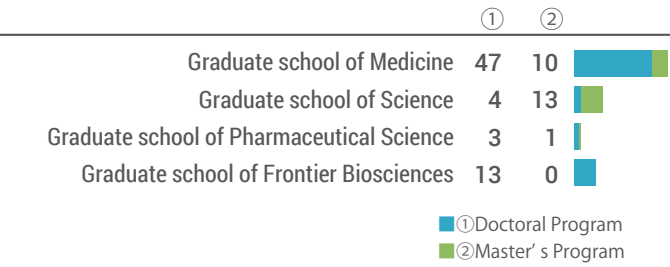
●Staffs



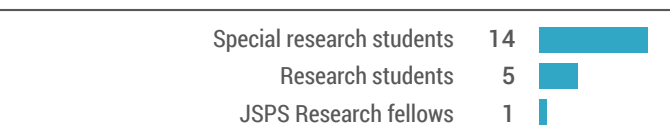
Total 199

(SA: Specially Appointed)

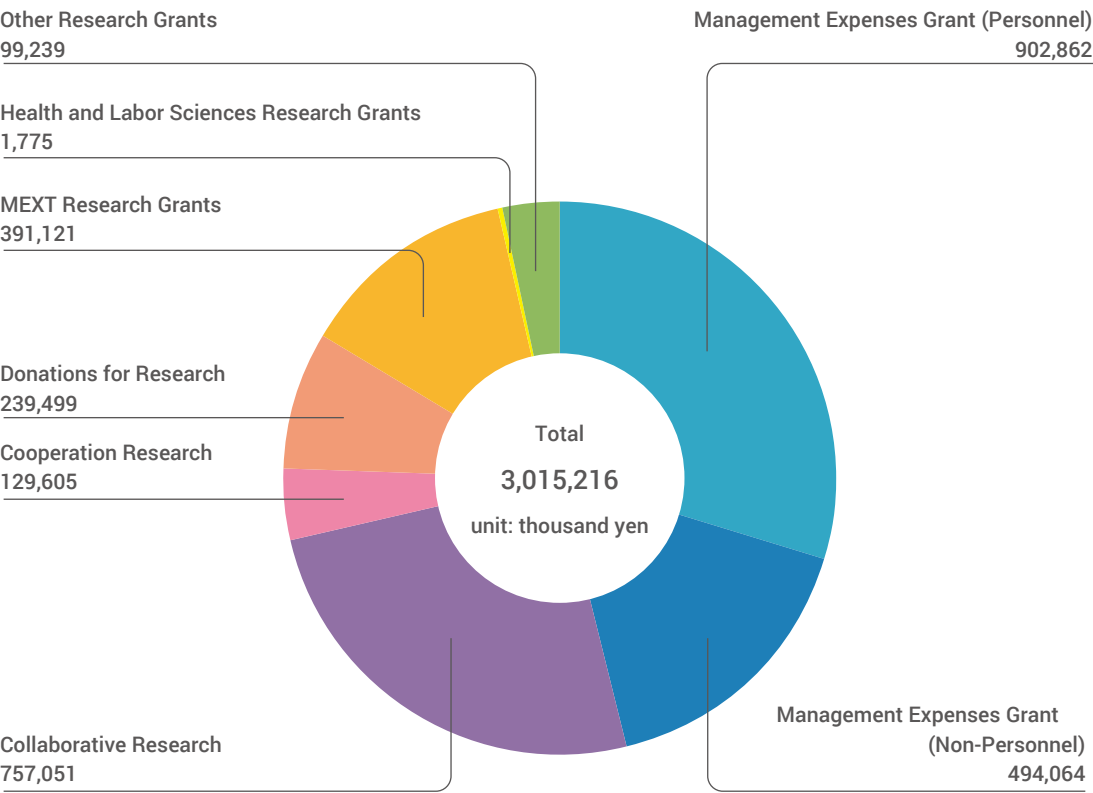
●Graduate Students



●Research Fellows and Research Students



ACCOUNTS



BUILDING AREA



① Main Building (left)  
⑪ Cutting-edge Research Building for Infectious Diseases (right)



② South Building



⑦ Central Laboratory for Biological Hazardous Microbes and (back)  
⑤⑥ Animal Resource Center (left,front)



Site Area 36,036㎡  
Building Area 8,702㎡ Gross Floor Area 39,945㎡

| Building name                                            | Total floor numbers | Building area (㎡) | Total floor area(㎡) |
|----------------------------------------------------------|---------------------|-------------------|---------------------|
| ① Main Building                                          | 7                   | 1,706             | 6,397               |
| ② South Building                                         | 2                   | 409               | 945                 |
| ③ North Building                                         | 3                   | 492               | 1,252               |
| ④ Annex                                                  | 2                   | 768               | 1,548               |
| ⑤ Animal Resource Center A                               | 2                   | 640               | 1,391               |
| ⑥ Animal Resource Center B                               | 4                   | 355               | 1,425               |
| ⑦ Central Laboratory for Biological Hazardous Microbes   | 3                   | 241               | 550                 |
| ⑧ Central Instrumentation Laboratory                     | 2                   | 378               | 504                 |
| ⑨ Depository for Dangerous Chemicals                     | 1                   | 160               | 160                 |
| ⑩ Integrated Life Science Building                       | 10                  | 1,072             | 9,258               |
| ⑪ Cutting-edge Research Building for Infectious Diseases | 9                   | 973               | 7,448               |
| ⑫ Animal Resource Center C (belonging to IFReC)          | 4                   | 738               | 2,482               |
| ⑬ IFReC Building                                         | 9                   | 770               | 6,585               |



# ACCESSMAP

▶ Osaka University  
Suita Campus



- |                                             |                                           |                                                       |
|---------------------------------------------|-------------------------------------------|-------------------------------------------------------|
| ① Research Institute for Microbial Diseases | ④ Graduate School of Medicine             | ⑦ Administration Bureau                               |
| ② Immunology Frontier Research Center       | ⑤ Graduate School of Frontier Biosciences | ⑧ The Institute of Scientific and Industrial Research |
| ③ Graduate School of Engineering            | ⑥ Osaka University Hospital               | ⑨ Osaka University Dental Hospital                    |



**Train**  
12-minute walk from "Kita-Senri" Station  
on Hankyu Senri Line.

**Monorail**  
20-minute walk from "Handai Byoin Mae" Station  
on Osaka Monorail Saito Line.

**Bus**

- From Senri-Chuo Station :  
5-minute walk from "Handai-Guchi" Bus Stop on Hankyu Buses heading to "Onohara Higashi", "Toyokawa-Eki", "Fujikasai".  
12-minute walk from "Handai Honbu Mae" Bus Stop on Hankyu Buses heading to "Handai Honbu Mae" or "Ibaraki Mihogaoka".
- From Hankyu Ibaraki-shi Station:  
12-minute walk from "Handai Honbu Mae" Bus Stop on buses heading to "Handai Honbu Mae" (via JR Ibaraki Station).



## Support RIMD Research

-Be part of the quest to find our more in science-

RIMD is the world's outstanding research institute in immunology, microbiology, oncology and biology. We have brought about drastic development in this field by identifying new pathogens and pathogenic mechanisms, vaccine development, oncogenic research. We work to support human resources development to promote advanced research in this field.  
Your support will enable to fuel innovative research in RIMD. Please contact us to learn more about how you can help Science tomorrow by supporting our research.

### How your donations are utilized

- Supporting RIMD researches overseas.
- Helping student to study in RIMD (Scholarships etc.)
- Helping international students to study in RIMD.
- Helping Training Course on Tropical Infectious Diseases for clinical doctors.
- Organizing scientific lectures and seminars for non-scientists

### [How to donate]

Credit card, Bank transfer

For detail please check the website

<https://www.miraikikin.osaka-u.ac.jp/english/>



Please make your donation for following projects at the Website  
<Institutes and Facilities>

- Research Institute for Microbial Diseases
- Research and Development of Malarial Vaccine Fund

