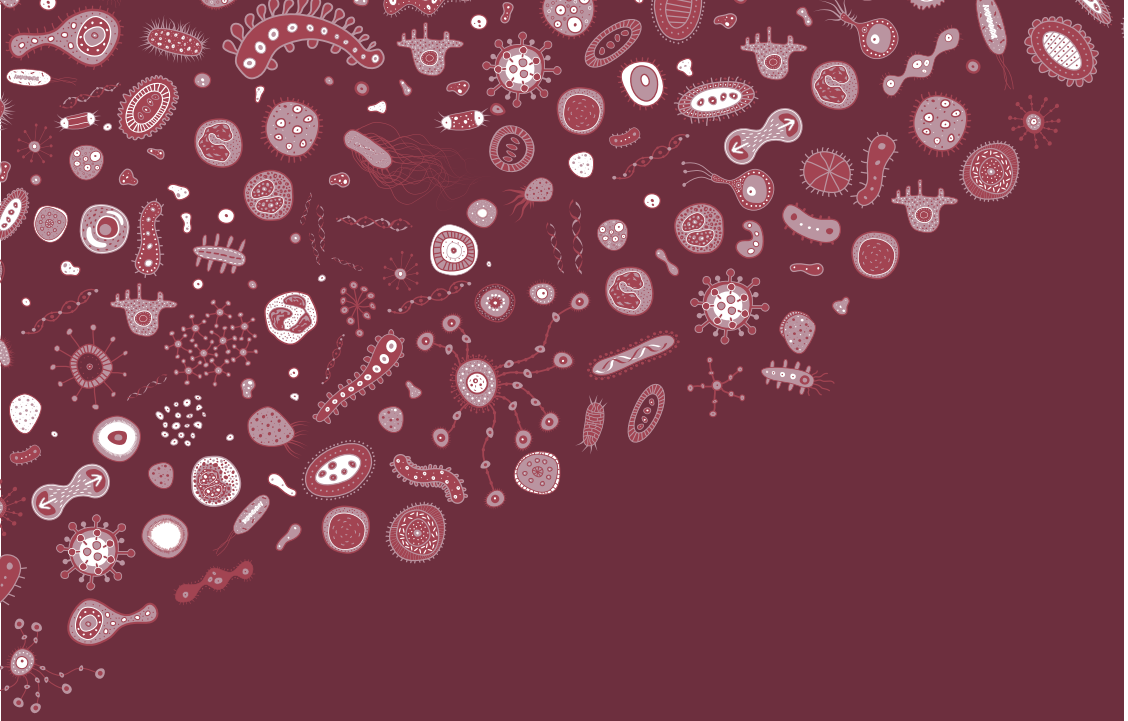

Osaka University

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Research Institute
for Microbial Diseases

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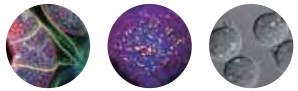

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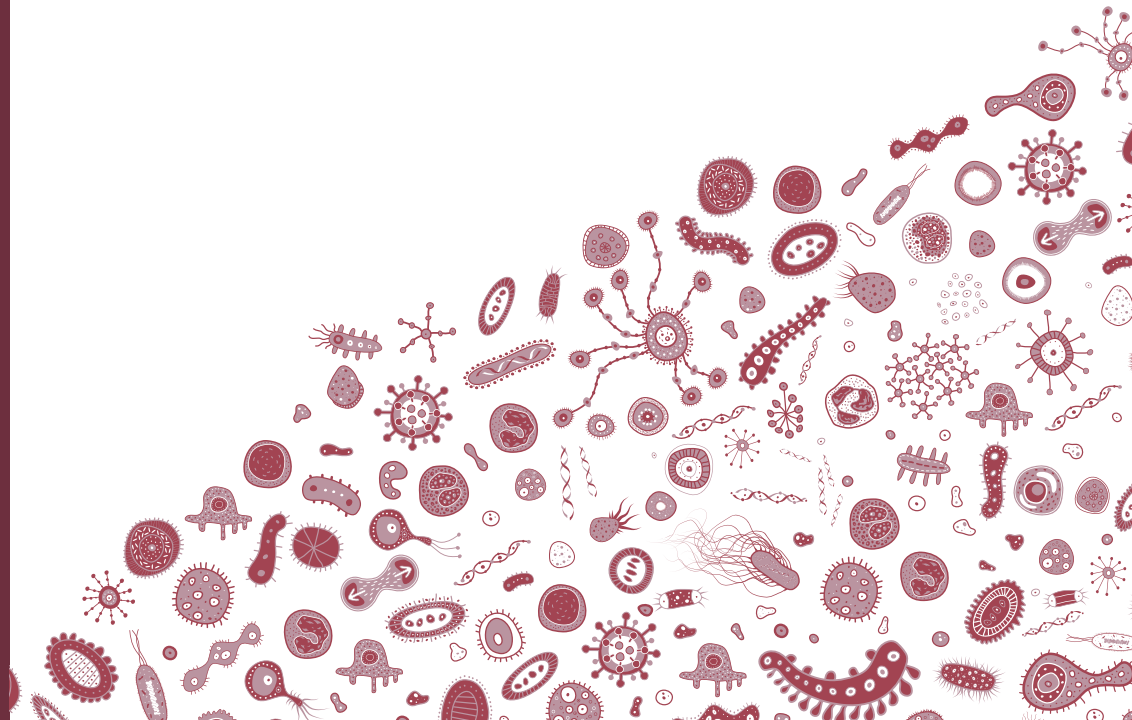


RIMD

Research Institute for Microbial Diseases

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.





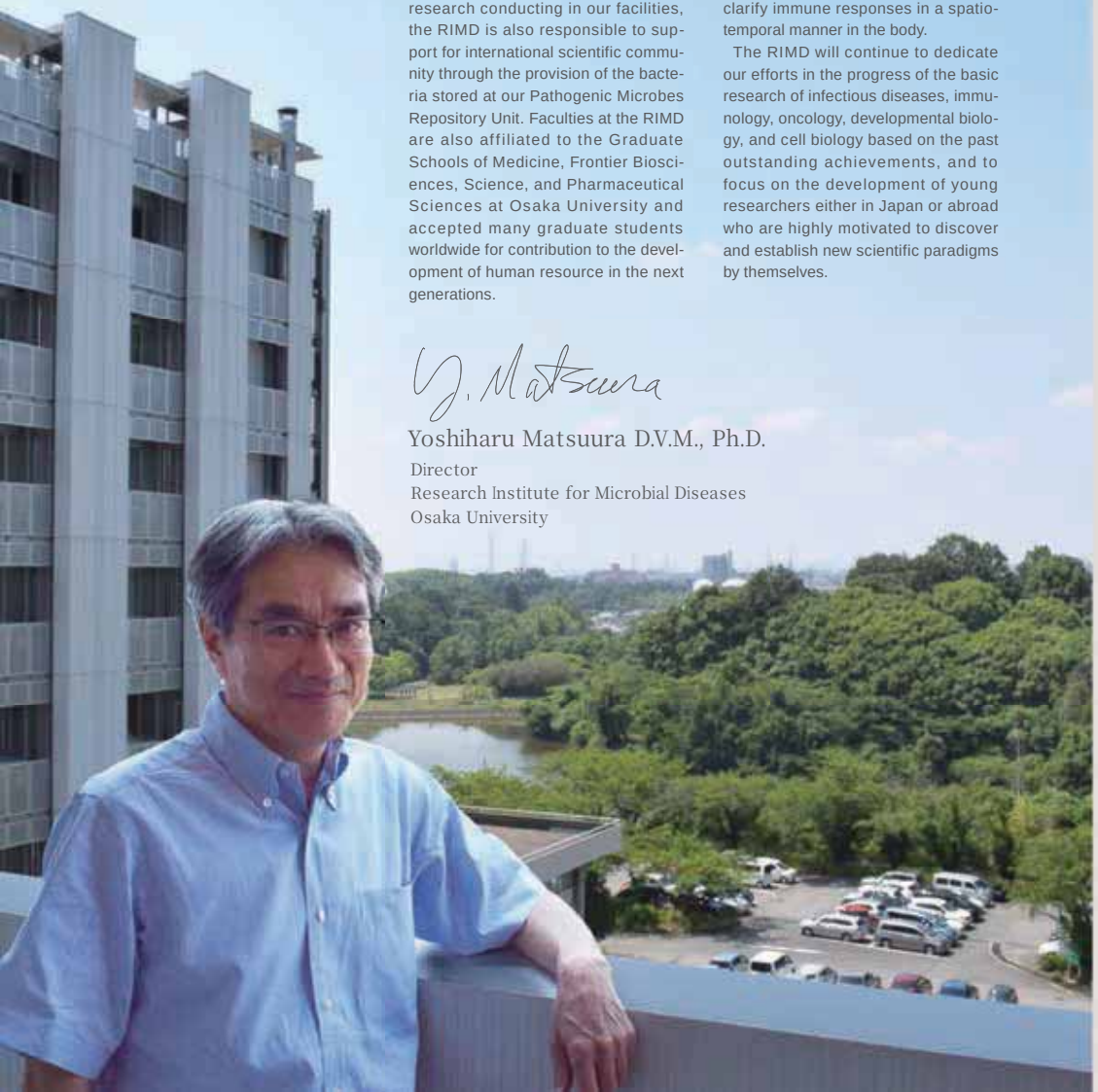
Message from the Director

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.

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.



Y. Matsuura

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

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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 Immunoparasitology — Yamamoto Lab

To explore the mechanisms that protect against microbes
Division of Host Defense
- Dept. of Molecular Immunology
- Dept. of Immunoregulation — Kinoshita Lab
- Dept. of Host Defense — Akira Lab
- Dept. of Immunochemistry — Arase Lab

To explore regulatory mechanisms in cancer cells
Division of Cellular and Molecular Biology
- Dept. of Molecular Microbiology — Hara Lab
- Dept. of Molecular Genetics — Nojima Lab
- Dept. of Oncogene Research — Okada Lab
- Dept. of Signal Transduction — Takakura Lab
- Dept. of Cellular Regulation — Miki Lab

Common Research Facilities
- Central Instrumentation Laboratory
- Radioisotope Laboratory
- Central Laboratory for Biological Hazardous Microbes
- Library

Office of Combined Program on Microbiology and Immunology
- Research Promotion Group
- Education Promotion Group

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 field and we also contribute extensively to growth in the basic sciences in Japan thorough 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

To understand our body system from genetic information
Genome Information Research Center
- Dept. of Experimental Genome Research — Ikawa Lab
- Dept. of Infection Metagenomics — Horii Lab

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 Combined Research on Microbiology and Immunology — Nagai Lab
- Lab. of Viral Replication — Kobayashi Lab
- Lab. of Pathogen Detection and Identification — Nakamura Lab
- Pathogenic Microbes Repository Unit

Animal Resource Center for Infectious Diseases

DNA-chip Development Center for Infectious Diseases

Research Collaboration Centers in Overseas

Research Collaboration Center for Infectious Diseases
RCC-ERI Domestic Labs
Mahidol-Osaka Center for Infectious Diseases

BIKEN Endowed Department of Dengue Vaccine Development

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

Division of Infectious Disease

Department of Molecular Bacteriology

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.

Prof.
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.

Staff

Assis. Prof. : Naoaki Shinzawa ／
Postdoc : Aya Fukui ／ Grad. Student: 4

To understand the mechanism of infection

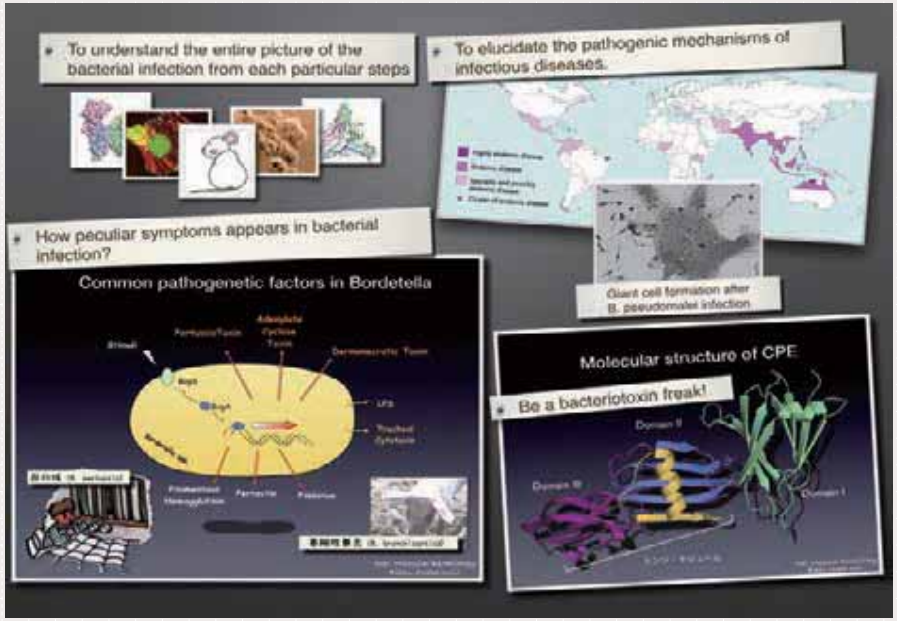
Bordetella pertussis, which is one of our research subjects is a representative pathogenic bacteria of *Bordetella* and causes whooping cough. In addition to *B. pertussis*, *B. parapertussis* and *B. bronchiseptica* are categorized in the genus *Bordetella*. Although these pathogenic organisms share 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.



Division of Infectious Disease

Department of Viral Infections

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).

Prof.
Tatsuo Shioda

Profile

Dr. Shioda obtaind his B. Sc. from the University of Tokyo in 1982 and his Ph.D. form 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 lipoatrophy 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 ABCC4 Is Associated with Tenofovir-Related Beta2-Microglobulinuria in Thai Patients with HIV-1 Infection. Likanonsakul 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.

Staff

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

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.

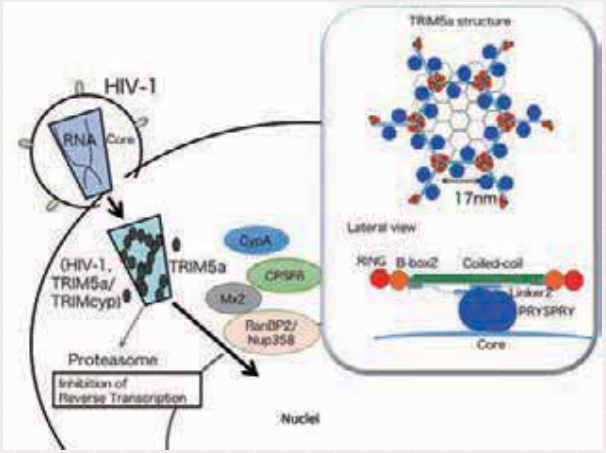


Fig. 1. Host factors involoving in early replication steps of HIV

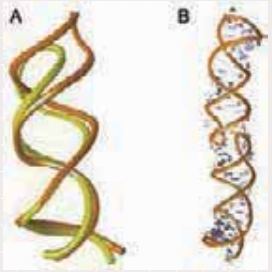


Fig. 2. Newly identified structure of DIS. A. Comparison of the current model (brown) with the previously proposed model (yellow). B. Structure in a dimeric form. The newly identified model shows more extended DIS structure possibly allowing stronger molecular interaction.

Division of Infectious Disease

Department of Molecular Virology

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.

Prof. 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 α-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 PA28γ 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

Assis. Prof. : Takasuke Fukuhara ／ Assis. Prof. : Toru Okamoto ／ Postdoc : Chikako Ono ／ JSPS PD : Tomokazu Tamura ／ Undergrad. Student 1 ／ Grad. Student 9

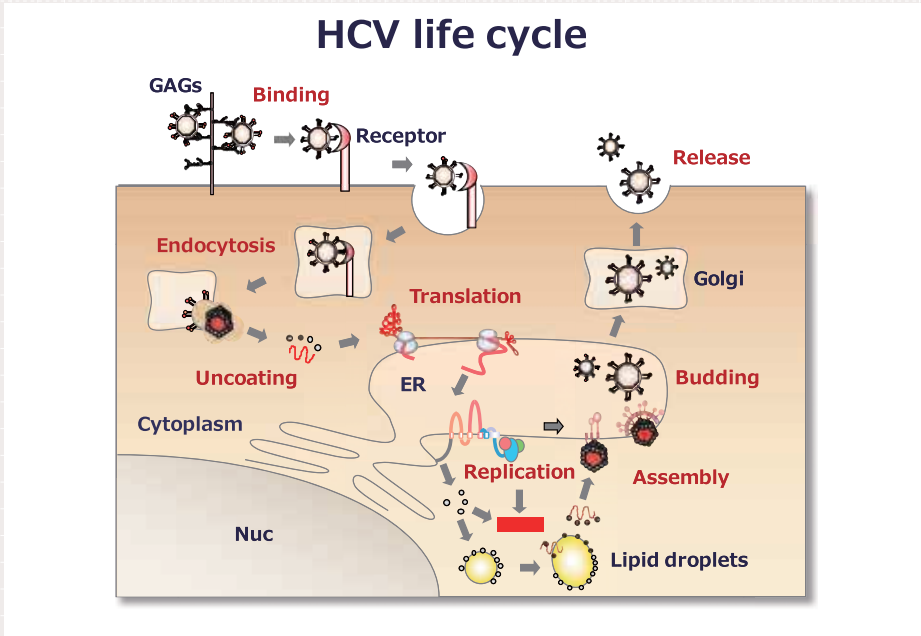
Molecular biology of hepatitis viruses

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.

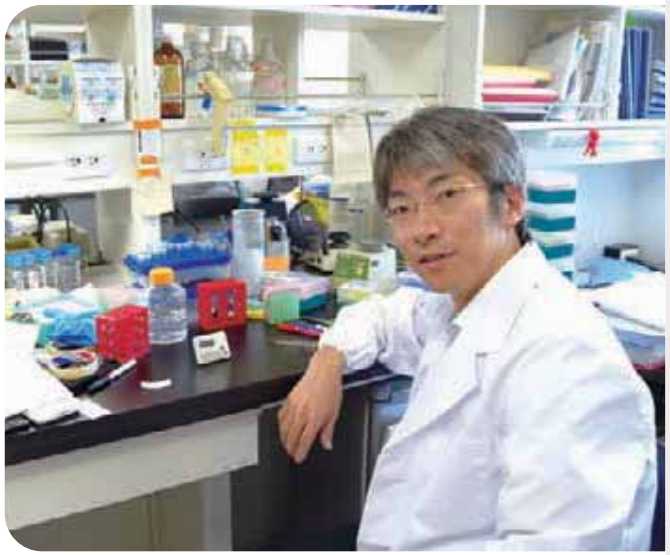


Division of Infectious Disease

Dept. of Immunoparasitology

In our immunoparasitology laboratory, we use the apicomplexan 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.

Prof.
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-γ-induced presentation of a *Toxoplasma* vacuolar antigen. Lee Y., et al. ***Cell Rep.*** (2015) 13:223-33.

(2) RabGDIα is a negative regulator of interferon-γ-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-γ-induced cell-autonomous responses against *Toxoplasma gondii*. Ohshima J., et al. ***J Immunol.*** (2014) 192: 3328-35.

(5) A cluster of interferon-γ-inducible p65 GTPases plays a critical role in host defense against *Toxoplasma gondii*. Yamamoto M., et al. ***Immunity*** (2012) 37:302-13.

(6) ATF6β is a host cellular target of the *Toxoplasma gondii* virulence factor ROP18. Yamamoto M., et al. ***J Exp Med.*** (2011) 208:1533-46.

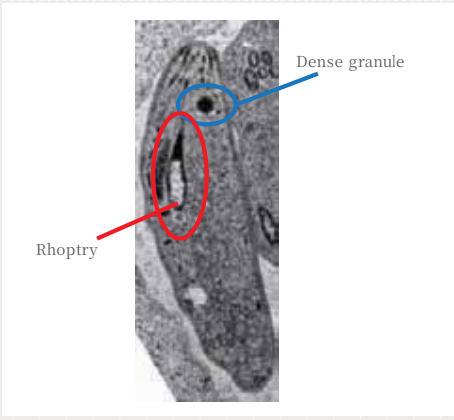
Staff

Assis. Prof. : Miwa Sasai ／ SA Assis.Prof. : Hironori Bando ／ SA Assis.Prof. : Jisu Ma ／ Grad. Student 2

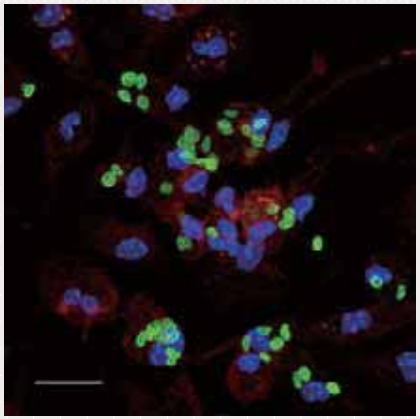
Antiviral host factors and their application to a cure for HIV infection

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-γ (IFN-γ) 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-γ-induced anti-*T. gondii* host defense mechanisms involved in innate and adaptive immunity. Recently, we found that IFN-γ-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-γ-induced immunity and autophagic pathways.

On the other hand, virulent *T. gondii* suppress IFN-γ-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).

Division of Host Defense

Dept. of Immunoregulation

Glycosylphosphatidylinositol (GPI) is a glycolipid that anchors proteins to plasma membranes. GPI-anchored proteins (GPI-APs) have various and important physiological functions in the body. Why do proteins have this peculiar structure? Our research goal is to elucidate the biogenesis, transport, and remodeling of GPI-APs and to understand the physiological significance of this linkage.

Prof.
Taroh Kinoshita (SUP)

Profile

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

Publication

(1) Pathogenic variants in PIGG cause intellectual disability with seizures and hypotonia. Makrythanasis P., et al. ***Am. J. Hum. Genet.*** (2016) 98:615-26.

(2) Post-Golgi anterograde transport requires GARP-dependent endosome-to-TGN retrograde transport. Hirata, T., et al. ***Mol. Biol. Cell*** (2015) 26: 3071-84.

(3) 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) 289:16835-43.

(4) 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.

(5) 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) 51:203-7.

(6) Significance of GPI-anchored protein enrichment in lipid rafts for the control of autoimmunity. Wang, Y., et al. ***J. Biol. Chem***. (2013) 288:25490-9.

Staff

Assoc. Prof. : Yusuke Maeda ／ Assoc. Prof. : Yohiko Murakami(SUP) ／ SA Assis.Prof. : Noriyuki Kanzawa ／ Postdoc : Tetsuya Hirata ／ Grad. Student 3

How are GPI-APs regulated?

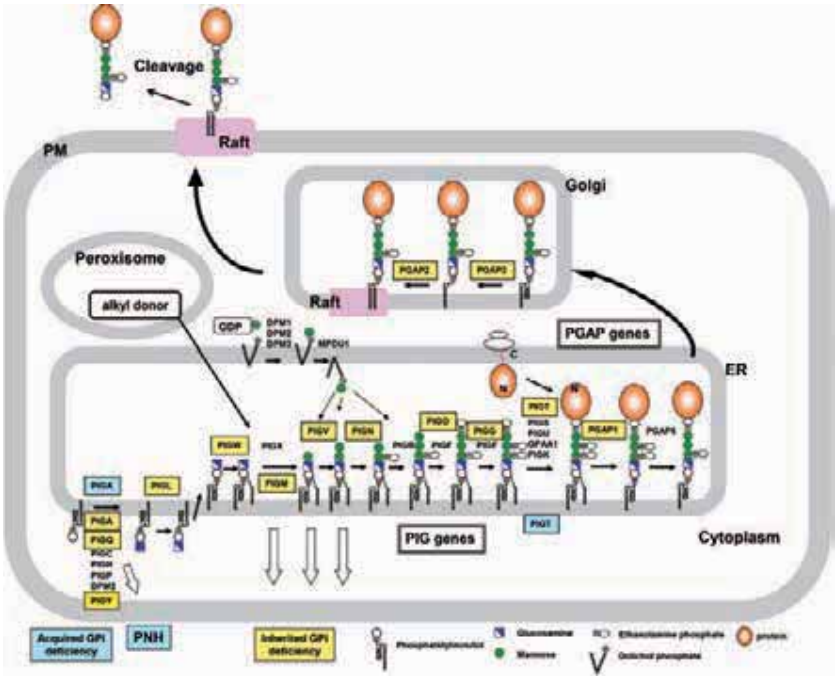
GPI anchors are synthesized in the endoplasmic reticulum (ER) and attached to the C terminus of proteins during post-translational modification. GPI-APs are transported from the ER to the Golgi and then to the cell surface in a way that is regulated according to the features of GPI. Recently, we identified the enzyme that cleaves GPI anchors and showed that GPI-APs are secreted and act on distant tissues. This result indicates that GPI anchors enable our body systems to regulate where and when these proteins work. We are currently studying the molecular mechanism that controls the functions of GPI-APs. In addition, GPI anchors have specific carbohydrate side-chains; intriguingly, the chain varies among cells and proteins. We are interested in the physiological significance of this carbohydrate chain and how it is synthesized in cells.

Molecular mechanisms underlying GPI deficiency

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

We also identified a disease called inherited GPI deficiency (IGD), which is caused by mutation of the GPI-anchor synthesizing enzyme, PIGM. Recent whole exome sequencing analysis using a next-generation sequencer identified 14 GPI-related gene mutations responsible for IGD.

To elucidate the molecular mechanisms underlying the pathogenesis of this disease, we developed a system to analyze GPI biosynthesis and modification. This system contributes to IGD research worldwide. Our aim is to elucidate how GPI anchors are involved in IGD and to find a way to treat this disease.



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

Division of Host Defense

Dept. of Host Defense

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:

Prof. Shizuo Akira (SUP)

Profile

Dr. Akira graduated Osaka University Medical School in 1997 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) Malt1-Induced Cleavage of Regnase-1 in CD4⁺ Helper T Cells Regulates Immune Activation. Uehata T., et al. ***Cell.*** (2013) 153(5):1036-49.

(2) Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. Satoh T., et al. ***Nature.*** (2013)495 (7442):524-8.

(3) Regnase-1, a Ribonuclease Involved in the Regulation of Immune Responses. Akira S. ***Cold Spring Harb Symp Quant Biol.*** (2013) 78:51-60.

(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): 1167-75.

(5) The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. Satoh T., et al. ***Nat Immunol.*** (2010) 11 (10):936-44.

(6) Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Matsushita K., et al. ***Nature.*** (2009) 458(7242):1185-90.

Staff

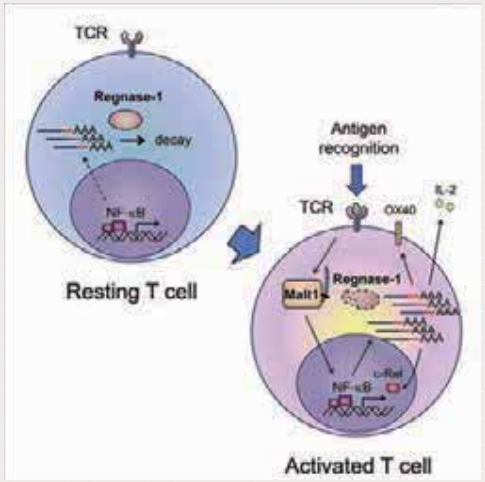
Assoc. Prof. : Kazuhiko Maeda ／ Assis. Prof. : Takashi Satoh ／ Postdoc : Kanako Kuniyoshi ／ Undergrad. Student 5 ／ Grad. Student 10

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

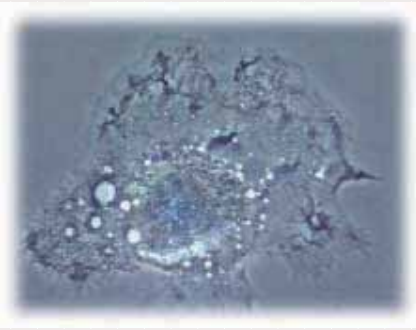
We have been investigating the comprehensive innate immune response induced by pattern recognition receptors that sense various pathogens. Recently, by studying the Toll-like receptor (TLR)-signaling pathway we found that a novel regulatory mechanism, “mRNA stability,” controls inflammatory responses. 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⁺ T cells suppresses autoimmune disease in mice.



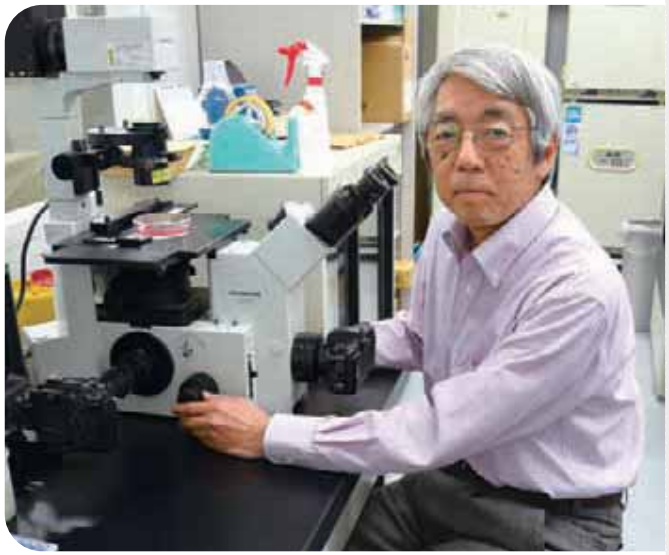
One subtype of disease-specific macrophage.

Division of Host Defense

Department of Cell Biology

For multicellular organisms, intercellular communication is an indispensable mechanism underlying homeostatic regulation of the whole organism. Cells deliver and receive various signals via extracellular factors, including growth factors and adhesion molecules. We are focusing on HB-EGF, a membrane-anchored growth factor, and its role in mechanisms underlying cell growth, morphogenesis. and cancer malignancy.

Prof. Eisuke Mekada



Profile

Dr. Mekada graduated Yamagata University in 1974 and received his Ph.D. from Osaka University in 1982. After working at RIMD, Institute for Molecular and Cellular Biology in Osaka university and Institute of Life Science in Kurume university, he was appointed Professor in RIMD in 2000. He served as the Director of RIMD from 2011 to 2015.

Publication

(1) Tetraspanin is required for generation of reactive oxygen species by the dual oxidase system in Caenorhabditis elegans. Moribe H., et al. ***PLos Genet.*** (2012) Sep;8(9):e1002957.

(2) HB-EGF and PDGF mediate reciprocal interactions of carcinoma cells with cancer-associated fibroblasts to support progression of uterine cervical cancers. Murata T., et al. ***Cancer Res.*** (2011) Nov 1;71(21):6633-42.

(3) Heparin-binding EGF-like growth factor is a promising target for ovarian cancer therapy. Miyamoto S., et al. ***Cancer Res.*** (2004) Aug 15;64(16):5720-7.

(4) Mice with defects in HB-EGF ectodomain shedding show severe developmental abnormalities. Yamazaki S., et al. ***J Cell Biol.*** (2003) Nov 10;163(3):469-75.

(5) Requirement of CD9 on the egg plasma membrane for fertilization. Miyado K., et al. ***Science*** (2000) Jan 14;287(5451):321-4.

(6) Heparin-binding EGF-like growth factor, which acts as the diphtheria toxin receptor, forms a complex with membrane protein DRAP27/CD9, which up-regulates functional receptors and diphtheria toxin sensitivity. Iwamoto R., et al. ***EMBO J.*** (1994) May 15;13(10):2322-30.

Staff

Assoc. Prof. : Ryo Iwamoto ／
Assis. Prof. : Hiroto Mizushima

Physiological role of HB-EGF and associated regulatory mechanisms

HB-EGF is a membrane-anchored growth factor that is proteolytically cleaved from the cell surface to yield a form (Fig. 1). Soluble HB-EGF functions in various biological processes involved in cell proliferation, differentiation, and inflammation. Analyses of HB-EGF knockout (KO) mice reveal that HB-EGF is expressed in several tissues and plays pivotal roles in many physiological processes. In particular, we are focusing on the role of HB-EGF in mouse cardiac valve development (Fig. 2). In this process, HB-EGF plays a role as a growth-inhibitory factor, though it is generally considered a growth-promoting factor in cancers. We are now analyzing the regulatory mechanisms that switch HB-EGF functions between growth promotion and growth inhibition.

Role of HB-EGF in cancer malignancy

HB-EGF is highly expressed in ovarian cancer tissues. Using a mouse xenograft model (Fig. 3), we found that over-expression of HB-EGF promotes tumor formation by ovarian cancer cells, and that inhibiting its expression suppresses tumor formation. Moreover, administration of CRM197, which neutralizes HB-EGF activity, suppresses tumor formation. Thus, factors inhibiting HB-EGF activity may be potent anti-ovarian cancer drugs. We are developing a new anti-ovarian cancer drug, called BK-UM (CRM197), which targets HB-EGF. Pre-clinical and clinical studies are underway.

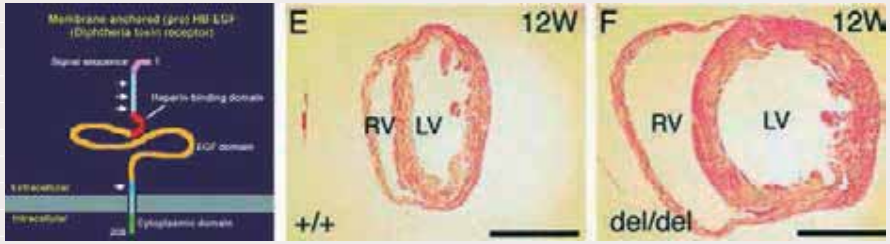


Fig. 1.
(Left) HB-EGF comprises an extracellular domain, a transmembrane domain, and an intracellular domain. HBF is cleaved and secreted from the cell surface. (Right) HB KO mice have an enlarged heart compared with wild-type mice.

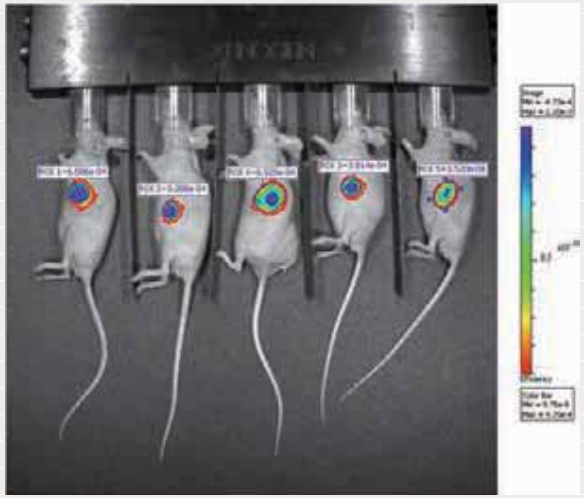


Fig. 2.
A murine cancer model. Cancer cells can be visualized using fluorescent proteins.

Division of Host Defense

Dept of Immunochemistry

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.

Prof.
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 PILRα 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) PILRα 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 ／ Assis. Prof. : Masako Kohyama ／
Postdoc : Fumiji Saito ／ Postdoc : Kazuki Kishida ／
Postdoc : Wataru Nakai ／ Undergrad. Student 2 ／ Grad. Student 7

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.

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).

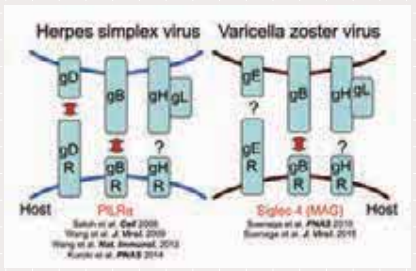


Fig. 1. Immune evasion of herpesviruses via paired inhibitory receptors.
Inhibitory receptors play an important role in immune regulation, whereas pathogens exploit inhibitory receptors for immune evasion. Especially, we have found that inhibitory receptors are used by herpesviruses to enter into host cells.

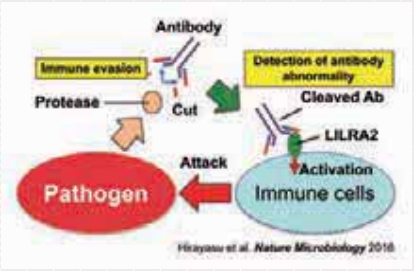


Fig. 2. Activating paired receptors play a role in host defense against bacterial infection
Activating paired receptor, LILRA2, recognizes immunoglobulin cleaved by bacterial protease activate innate immune cells (Hirayasu et al. *Nat. Microbiol.* 2016).

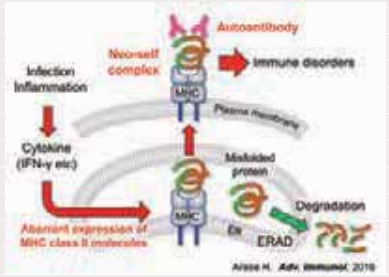


Fig. 3. Misfolded proteins complexed with MHC class II molecules are targets for autoantibodies.
Misfolded cellular proteins are transported to the cell surface without being processed to peptides by associating with MHC class II molecules in the ER. Furthermore, misfolded proteins complexed with MHC 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).

Division of Cellular and Molecular Biology

Department of Molecular Microbiology

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.

Prof.
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. (Postdoctoral 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^{Cdh1} 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 ／ Assis. Prof. : Shimpei Kawamoto ／
JSPS PD : Masaki Takasugi ／ Postdoc : Masahiro Wakita ／
Grad. Student 2

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.

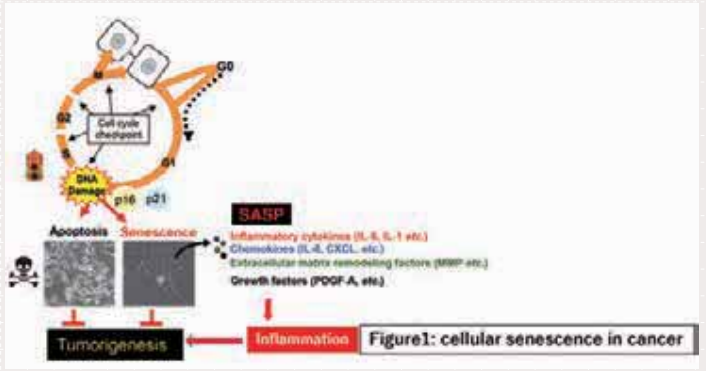
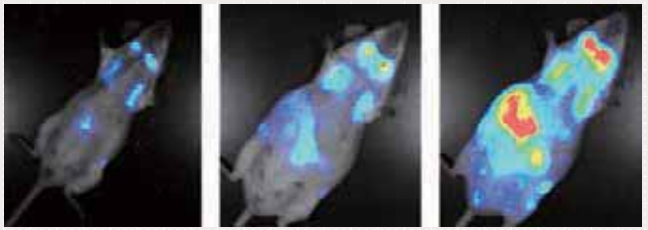


Fig. 1.
Cellular senescence initially inhibits proliferation of damaged cells, thereby acting as a fail-safe mechanism. However, in the long term, senescent cells may eventually promote tumorigenesis via SASPs.

Figure1: cellular senescence in cancer



6 weeks　　12 months　　20 months

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

Division of Cellular and Molecular Biology

Department of Molecular Genetics

We are studying the molecular mechanisms underlying Lats1 (large tumor suppressor 1), Lats2, cyclin G, and GAK (cyclin G-associated kinase) activity to understand how chromosomal instability occurs in cancer cells.

Prof. Hiroshi Nojima

Profile

Dr. Nojima received his PhD from Tokyo University in 1979 and worked as a postdoc at Stanford University, School of Medicine for 3 years before returning to Japan to be employed by Jichi Medical School. He spent 7 years at Jichi Medical School as Assitant (1981-1982) and Lecturer (1982-1988). He was appointed as Associate Professor at RIMD in 1988 and became Professor in 1995.

Publication

(1) Lats1 suppresses centrosome overduplication by modulating the stability of Cdc25B. Mukai S., et al. *Sci Rep* (2015) 5:16173.

(2) ELAS1-mediated inhibition of the cyclin G1-B'γ interaction promotes cancer cell apoptosis via stabilization and activation of p53. Ohno S., et al. *Oncogene* (2015) 34(49):5983-96.

(3) Phosphorylation of CHO1 by Lats1/2 regulates the centrosomal activation of LIMK1 during cytokinesis. Okamoto A., et al. *Cell Cycle* (2015) 14(10):1568-82.

(4) Lats2 phosphorylates p21/CDKN1A after UV irradiation and regulates apoptosis. Suzuki H., et al. *J Cell Sci* (2013) 126(Pt 19):4358-68.

(5) N-terminal truncation of Lats1 causes abnormal cell growth control and chromosomal instability. Yabuta N., et al. *J Cell Sci* (2013) 126(Pt 2):508-20.

(6) Neonatal lethality in knockout mice expressing the kinase-dead form of the gefitinib target GAK is caused by pulmonary dysfunction. Tabara H., et al. *PLoS One* (2011) 6(10):e26034.

Staff

Assoc. Prof. : Yabuta Norikazu ／
Assis. Prof. : Daisuke Okuzaki (SUP) ／
Postdoc : Yoko Naito ／ Grad. Student 3

Lats group

Lats1 and Lats2 are pivotal serine/threonine kinases that regulate the cell cycle checkpoint, whereas the Hippo pathway mainly regulates organ size and cell growth. We found that Lats1/2 kinases play pivotal roles in chromosome stability through stringent regulation of cell proliferation and mitotic progression. For example: (A) Mouse embryonic fibroblasts (MEFs) derived from *Lats1* knockout (KO) and *Lats2* KO mice display severe mitotic defects, such as centrosome amplification/fragmentation, abnormal chromosome segregation, and aberrant cytokinesis; (B) Lats1 regulates precise centrosome duplication and chromosome segregation by regulating the stability of a protein phosphatase, Cdc25B; (C) MEFs from mice in which Lats1 is knocked out by disrupting its N-terminal region (*Lats1*$^{DN/DN}$) display chromosome missegregation, polyploidy (an increase in the number of multinucleated cells), and anchorage-independent growth, which is a hallmark of malignancy; (D) we identified two novel Lats2-mediated signaling pathways, the ALB and CLP pathways (Fig. 1); (E) recently, we reported that Lats1/2 phosphorylate a kinesin-like motor protein, CHO1, which regulates cytokinesis on the centrosome; (F) the activated form of Lats2 phosphorylates p21/CDKN1A, inducing apoptosis under conditions of severe DNA damage; and (G) we are currently analyzing the molecular mechanisms by which Lats1/2 regulate EMT and cancer stem cells to identify new diagnostic markers for invasive cancers.

Cyclin G (CycG1 and CycG2) group

We previously discovered that CycG1 associates with the B'γ subunit of protein phosphatase 2A (PP2A) to recruit PP2A to target proteins such as p53 and MDM2. A 29 amino acid peptide, named ELAS1 [i:lΛz wΛn], triggers apoptosis in cancer cells by promoting de-phosphorylation of Mdm2-pT216 and p53-pS46 via inhibition of CycG1-B'γ association (Fig. 2). At present, our basic research is focused on clinical application of ELAS1.

GAK (cyclin G-associated kinase) group

GAK plays an essential role in membrane trafficking by regulating clathrin uncoating in the cytoplasm. We discovered the following additional functions of GAK: (A) GAK forms a complex with CycG1 and B'γ and phosphorylates B'γ–pT104 to regulate PP2A activity; (B) GAK localizes at the centrosome and nucleus to regulate centrosome maturation and chromosomal condensation/alignment, respectively; (C) GAK kinase dead knockout mice (GAK-kd-/-) exhibit neonatal lethality, with pulmonary dysfunction (Fig. 3); and (D) recently, we discovered several phosphorylation targets of GAK and found that these play important roles in proper progression of M phase.

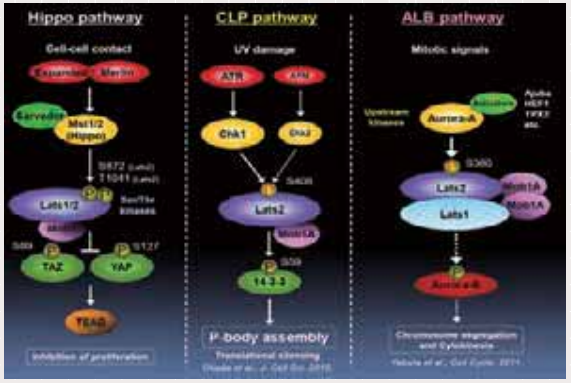


Fig1. Lats1/2 signal transduction pathway. Hippo pathway to inhibit cell growth, CLP pathway to inhibit traslation and ALB pathway to regulate chromosome segregation and cytokinesis.

Fig. 2. ELAS1 targets 2 molecules

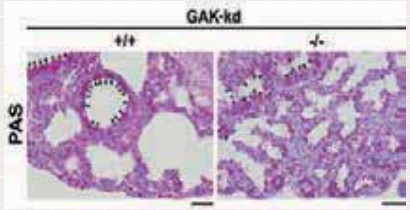


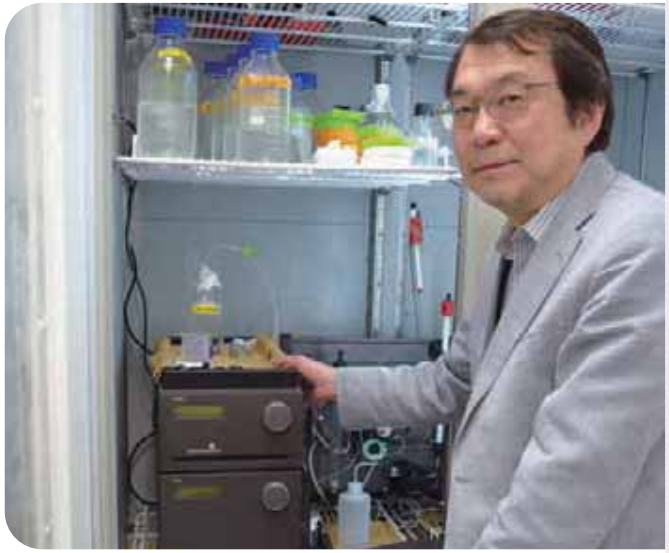
Fig. 3. GAK Kinase KO mice shows developmental failure in the lung

Division of Cellular and Molecular Biology

Department of Oncogene Research

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.

Prof.
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. ***Oncognesis*** (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. Kawabuchu M., et al. ***Nature*** (2000) 404:999-1003

Staff

Assoc. Prof. : Shigeyuki Nada ／ Assis. Prof. : Kentaro Kajiwara ／ Postdoc : Akira Ogawa ／ Undergrad. Student 5 ／ Grad. Student 14

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.

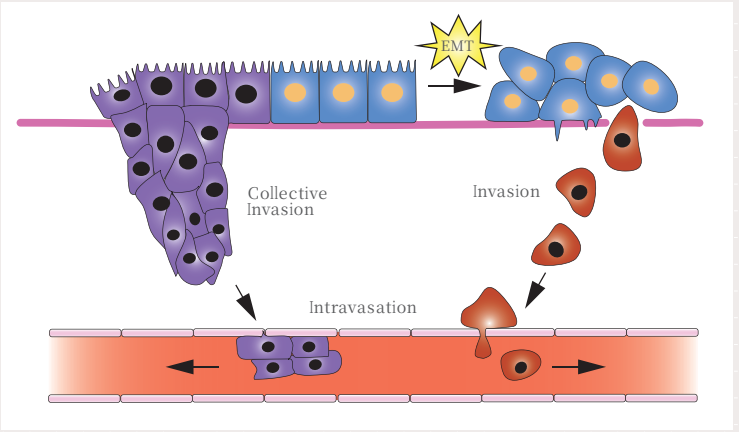


Fig. 1. Invasion and metastasis of cancer cells

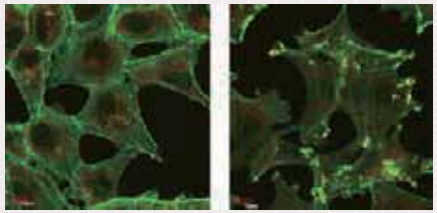


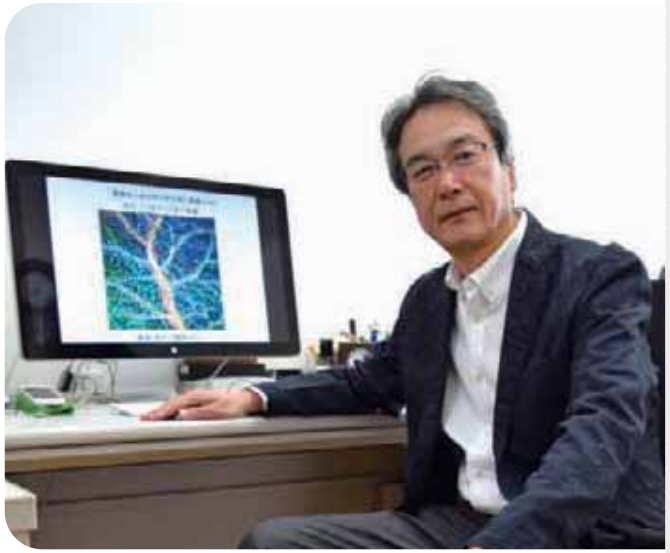
Fig. 2. Src activation induces morphological changes and increases cell mobility.

Division of Cellular and Molecular Biology

Department of Signal Transduction

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.

Prof. 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

Assis. Prof. : Hiroyasu Kidoya ／ Assis. Prof. : Hisamichi Naito ／
Postdoc : Weizhen Jia ／ Undergrad. Student 1 ／ Grad. Student 11

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.

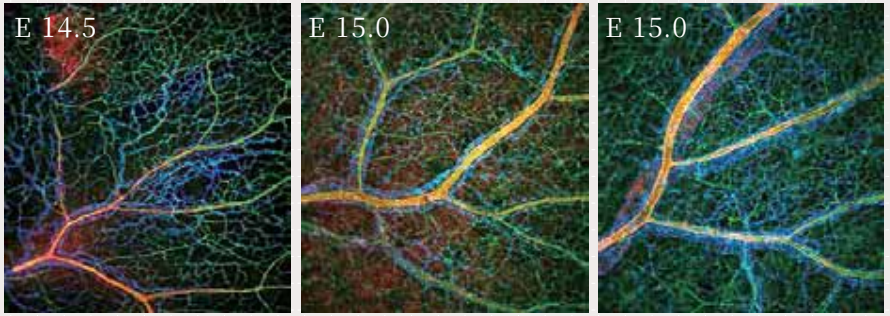


Fig. 1. Vascular development in mouse embryos. Hierarchal architecture of blood vessels accompanied by arterial (yellow)–venous (blue) alignment. Green; endothelial cells.

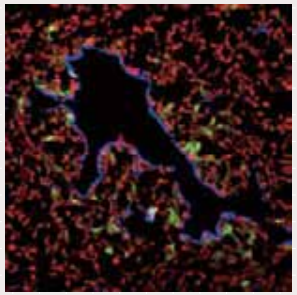


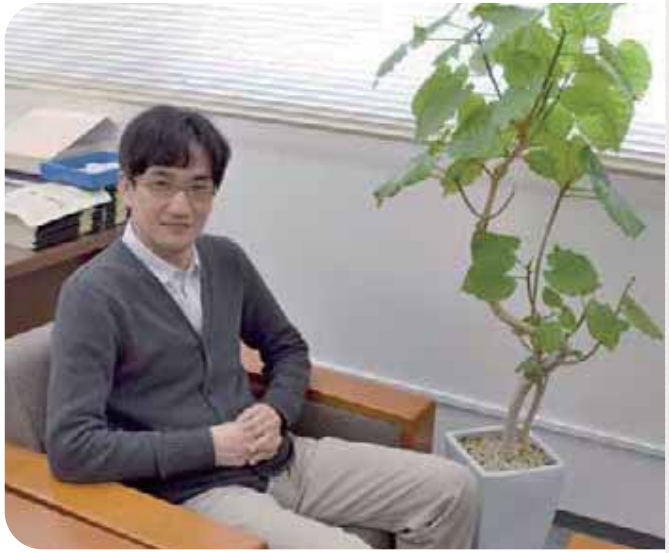
Fig. 2. Endothelial cells (blue) and CSCs (green) in a tumor.
CSCs localize at the perivascular area, the so called “vascular niche.”

Division of Cellular and Molecular Biology

Department of Cellular Regulation

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.

Prof.
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, Universuty of Tokyo and at the Institute for Protein Research, Osaka University.

Publication

(1) 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

(2) Membrane protein CNNM4-dependent Mg^{2+} efflux suppresses tumor progression. Funato Y., et al. ***J Clin Invest.*** (2014) 124(12):5398-410

(3) 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

(4) Thioredoxin mediates oxidation-dependent phosphorylation of CRMP2 and growth cone collapse. Morinaka A., et al. ***Sci Signal.*** (2011) 4 (170):ra26

(5) Nucleoredoxin sustains Wnt/β-catenin signaling by retaining a pool of inactive dishevelled protein. Funato Y., et al. ***Curr Biol.*** (2010) 20(21):1945-52

Staff

Assis. Prof. : Daisuke Yamazaki ／ Assis. Prof. : Yosuke Funato ／
Postdoc : Osamu Hashizume ／ Undergrad. Student 3 ／ 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.

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.

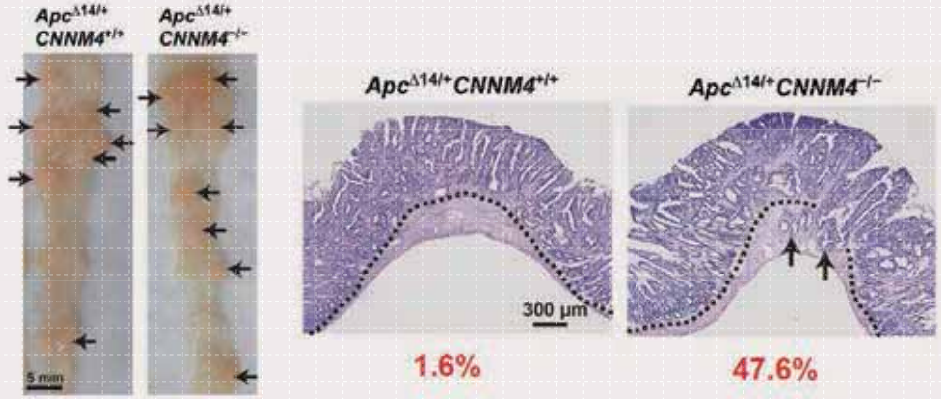


Fig. 1. Macroscopic images of the intestine (left) and histological images of polyps (right) in the indicated genetically engineered mice. *CNNM4*-deficient mice develop adenocarcinomas that invade the muscle layer (arrows).

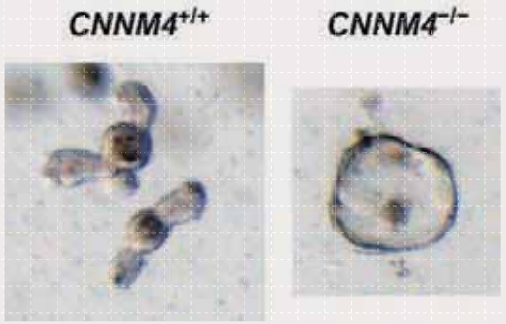


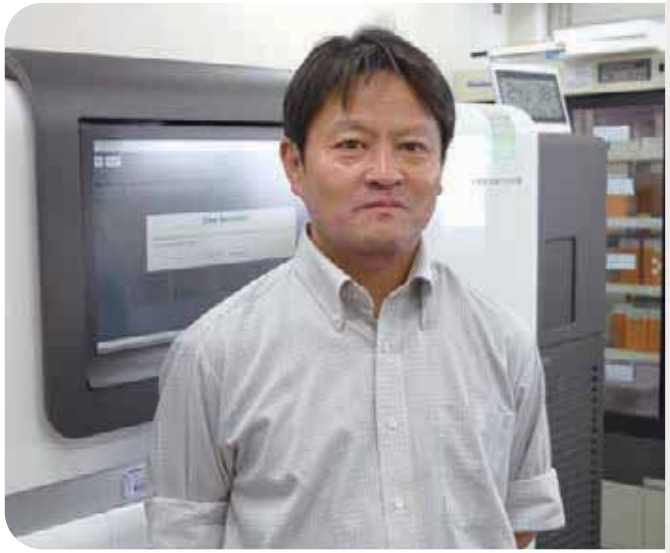
Fig. 2. Organoid culture of intestinal epithelia from the indicated genetically engineered mice. *CNNM4* deficiency causes morphological abnormalities.

Research Center for Infectious Disease Control

Department of Bacterial Infections

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.

Prof. 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^+-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 ／
Assis. Prof. : Shigeaki Matsuda

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.

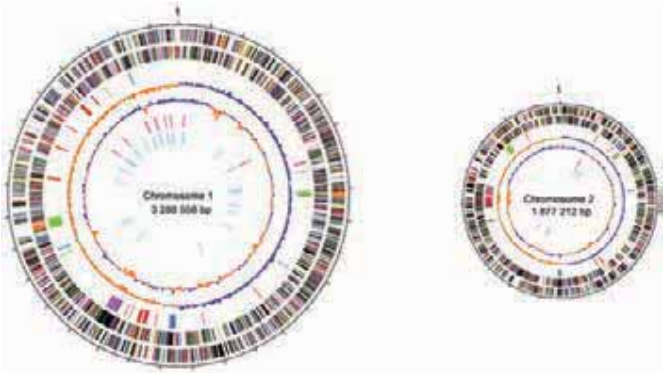


Fig. 1. The genomes of bacteria belonging to genus *Vibrio* comprise two distinct circular chromosomes.

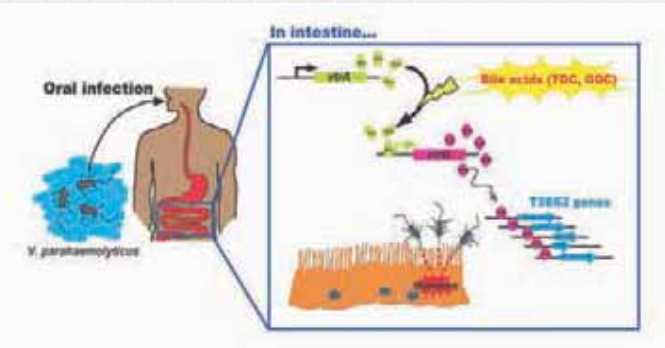


Fig. 2. Bile in the small intestine induces expression of genes encoding T3SS2, which is the major virulence factor produced by *Vibrio parahaemolyticus*, the causative agent of diarrhea.

Research Center for Infectious Disease Control

Department of Molecular Protozoology

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 on our own candidate vaccine antigen gene and conducting clinical trials.

Prof.
Toshihiro Horii

Profile

Dr. Horii received his Ph.D. from Osaka University in 1981. After working at School 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

Assis. Prof. : Nobuko Arisue ／ Assis. Prof. : Takahiro Tougan ／
SA Professor : Eisaku Kimura ／ SA Associate Professor : Nirianne M. Q. Palacpac ／
Postdoc : Jyotheeswara Reddy Edula

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 expressed by newly “born” malaria parasites that then invade red blood cells to produce the next generation. Epidemiological studies in malaria hyper-endemic areas showed that children with antibodies against SERA5 are resistant to symptomatic malaria infection, although 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. However, we observed good antibody responses in young Ugandan children that experienced fewer malarial infections. Indeed, we obtained 72% protective efficacy 1 year post-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 in 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 Procedure) conditions at the Kanonji Institute of The Research Foundation for Microbial Diseases of Osaka University.

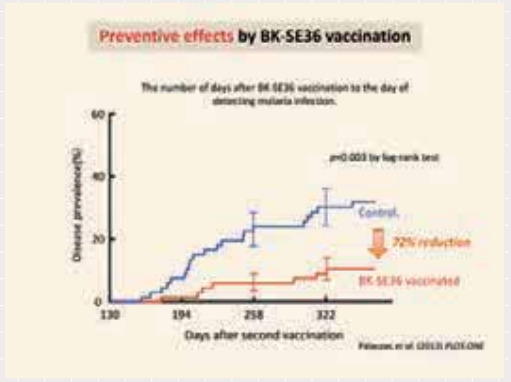
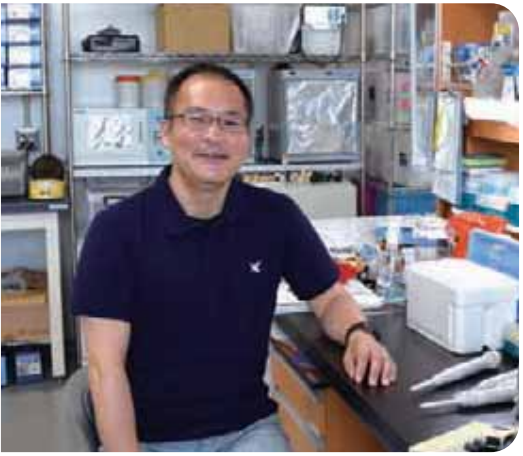


Fig. 2.
Kaplan-Meier curves for 6- to 20-year-olds at 130–365 days post-second vaccination with BK-SE36.

International Research Center for Infectious Diseases

Laboratory of Clinical Research on Infectious DIseases

SA Assoc. prof.
Wataru Kamitani



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

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.

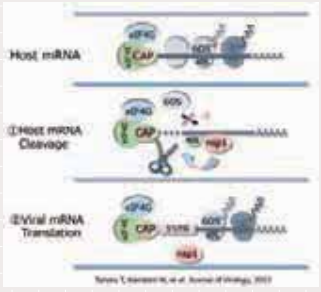
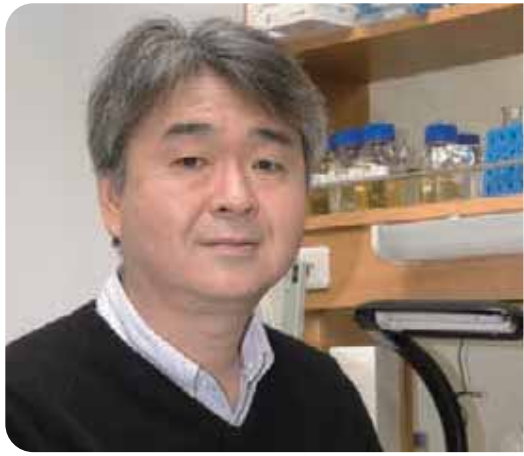


Fig. Gene expression control by SARS-CoV nsp1
①Nsp1 binds to 40S ribosome, and then induces translational shutoff. The nsp1-40S binding induces cleavage of mRNA.
②Nsp1 binds to viral mRNA, and then the interaction enhances viral replication.

International Research Center for Infectious Diseases

Laboratory of Combined Research on Micobiology and Immunology

Assoc. prof.
Hiroki Nagai



Profile

Dr. Nagari received his Ph.D. from Kyoto University in 1991. He joined Institute for Virus Research in Kyoto university until 1992 and became a Research Associate in National Institute of Genetics in the same year. He worked as a Postdoctoral Associate and Associate Research Scientist at Yale School of Medicine from 199 to 2004 before he appointed SA Associate Professor at RIMD in 2004. He took his current position in 2011.

Publication

(1) The Type IVB secretion system: an enigmatic chimera. Kubori T., et al. ***Curr Opin Microbiol*** (2016) 29:22-9

(2) Molecular and structural analysis of ***Legionella*** DotI gives insights into an inner membrane complex essential for type IV secretion. Kuroda T., et al. ***Sci Rep*** (2015) 5:10912

(3) Hijacking the host proteasome for the temporal degradation of bacterial effectors. Kubori T., et al. ***Methods Mol Biol*** (2014) 1197:141-52

Many pathogenic and endosymbiotic bacteria survive within eukaryotic host cells. *Legionella pneumophila* is one such intracellular bacteria, ubiquitously found in fresh water environments. In nature, *Legionella* survives and replicates within free-living amoeba (e.g., *Acanthamoeba*). When inhaled by humans, *Legionella* enters alveolar macrophages and establishes a replicative niche. Infections eventually cause a severe form of pneumonia, known as Legionnaires' disease.

Deciphering the molecular basis upon which *Legionella* survive within cells

The type IV secretion system (T4SS) is a bacterial secretion system that transports biological macromolecules such as nucleic acids and proteins and is evolutionally closely related to bacterial conjugation systems. *Legionella* utilizes Dot/Icm T4SS to deliver hundreds of bacterial "effector proteins" into host cells, a process essential for intracellular survival and pathogenesis. Phylogenetic analyses of the order *Legionellales*, which includes *Legionella* species and a zoonotic pathogen called *Coxiella burnetii*, demonstrate that a common ancestor acquired a T4SS on its chromosome, and that T4SSs are maintained by vertical gene transfer. Thus, T4SSs and effector proteins play a critical role in pathogenesis/endosymbiosis; however, the underlying molecular basis remains largely unknown. We have been working to address the question of how intracellular bacteria like *Legionella* establish replicative niches in hostile environments, such as those inside eukaryotic cells.

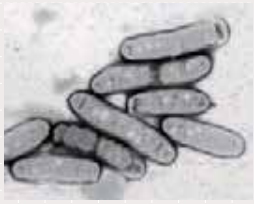


Fig. 1. *Legionella pneumophila*

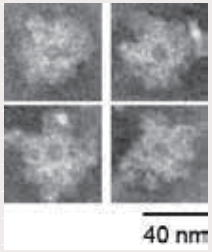


Fig. 2. T4SS core complex

International Research Center for Infectious Diseases

Laboratory of Viral Replication

SA Assoc. prof.
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.

Publication

(1) 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

(2) 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

(3) 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) Oncolytic viral therapy using reovirus

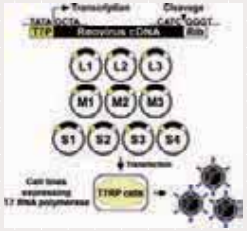
Mammalian orthoreoviruses (reoviruses) are members of the family *Reoviridae* and contain a 10-segmented genome comprising double-stranded (ds) RNA. Reoviruses are highly tractable experimental models for studies of dsRNA virus replication and pathogenesis. In the last decade, reoviruses have been evaluated in both animal models and humans as oncolytic agents against a variety of tumors, including head and neck, colon, breast, and pancreatic cancers. 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 show limited efficacy. We are developing safer and more effective reovirus-based cancer therapeutics via genetic modification.

2) Highly pathogenic bat-borne reovirus

Bats are a natural reservoir for many important zoonotic viruses, including Hendra virus, Nipah virus, and possibly Severe Acute Respiratory Syndrome (SARS) coronavirus and Ebola virus. Nelson Bay reovirus (NBV) was isolated from a flying fox in 1968, but was not associated with any disease. Recently, Melaka virus, which is genetically closely related to NBV, was isolated from a human patient in Malaysia suffering from an acute respiratory tract infection (RTI). Subsequently, other related strains of bat-associated orthoreoviruses have been isolated in Malaysia, Indonesia, and China. We also isolated and characterized another new NBV, called Miyazaki virus, from a patient with acute RTI after returning to Japan from Indonesia in 2007. These isolates raise concerns about bat-transmitted orthoreovirus infections in humans. We are currently investigating how NBV replicates and causes disease using a combination of genetic, biochemical, and biophysical approaches with an aim to developing vaccines, diagnostic tools, and therapeutic agents.

3) Other reoviruses

Members of the family *Reoviridae* include rotaviruses (important gastrointestinal pathogens in both humans and animals) and avian reoviruses (economically important diseases in commercial poultry flocks). We are also studying these viruses to better understand their replication, protein expression/function, and effect on cell biology.



Strategy to generate reovirus from cloned cDNAs
The ten reovirus cDNAs are transfected into murine L cells expressing T7 RNA polymerase.

International Research Center for Infectious Diseases

Pathogenic Microbes Repository Unit

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.

Staff

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

Genome Information Research Center

Department of Experimental Genome Research

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.

Prof.
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) 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.

(2) Structural and functional insights into IZUMO1 recognition by JUNO in mammalian fertilization. Kato K., et al. ***Nat Commun.*** (2016) 7:12198.

(3) 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.

(4) Generation of Hprt-disrupted rat through mouse←rat ES chimeras. Isotani A., et al. ***Sci Rep.*** (2016) 6:24215.

(5) Sperm calcineurin inhibition prevents mouse fertility with implications for male contraceptive. Miyata H., et al. ***Science.*** (2015) 350(6259):442-5.

(6) Generation of mutant mice by pronuclear injection of circular plasmid expressing Cas9 and single guided RNA. Mashiko D., et al. ***Sci Rep.*** (2013) 3:3355.

Staff

Assis. Prof.：Yuhkoh Satouh (SUP) ／ Assis. Prof.：Yoshitaka Fujihara ／ Assis. Prof.：Haruhiko Miyata ／ Assis. Prof.：Masashi Mori ／ SA Assistant Professor：Daiji Kiyozumi (SUP) ／ JSPS Postdoc：Taichi Noda ／ Postdoc：Keisuke Shimada ／ Postdoc：Julio Manuel Castaneda ／ Postdoc：Kanako Kita ／／ Undergrad 3 ／ Graduate MA1・Ph.D.4 ／ Visiting Researcher：Masaru Okabe ／ Guest Professor：Martin M. Matzuk ／ Guest Assoc. Professor：Ayako Isotani

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 developed 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.

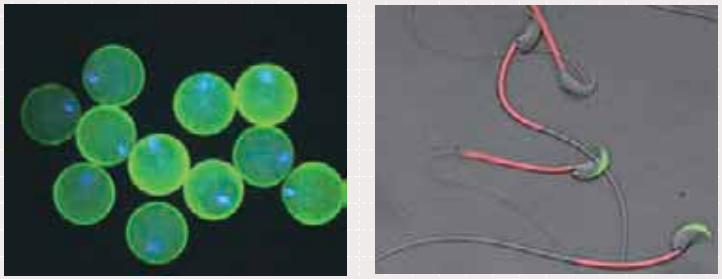


Fig. 2. Mouse eggs (left) and sperm (right) labeled with fluorescent proteins. These gametes are used to visualize the fertilization process. (Figs from Exp. Anim. 59(1), 105-7, 2010)

Genome Information Research Center

Department of Infection Metagenomics

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
Prof.
Toshihiro Horii (SUP)

Prof.
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

SA Associate Professor : Shota Nakamura (SUP) ／
Associate Professor : Naohisa Goto (SUP) ／
SA Assis. prof. : Daisuke Motooka ／ Postdoc : Mizue Anda

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.

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.

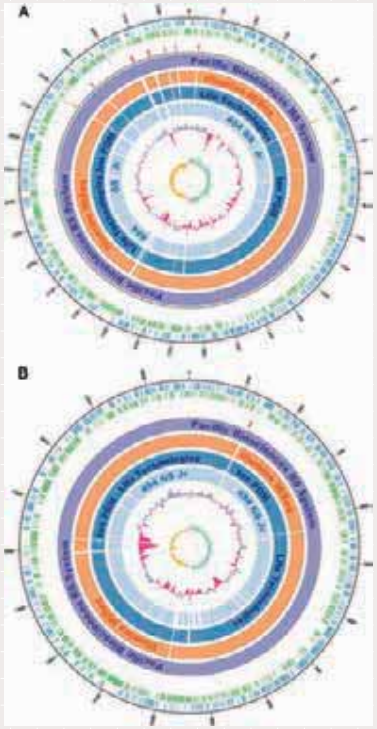


Fig. 2.
Genomic analysis of *Vibrio parahaemolyticus* using four models of next-generation sequencer: 454 GS Jr(Roche)、IonPGM(Life Technologies)、MiSeq(Illumina)、Pacific Biosciences RS System (PacBio)
GS Jr, MiSeq, and IonPGM produce short reads. Therefore, they require assembly of short fragments. The 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.

Assoc. prof. 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+/Ca2+ 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 (SmαA) gene (Fig. 2). Several cis-acting DNA elements and transcriptional nuclear factors essential for SmαA expression have been identified. Since SmαA is also expressed in many tissues during acute inflammation, we are examining expression of the SmαA and its function(s).

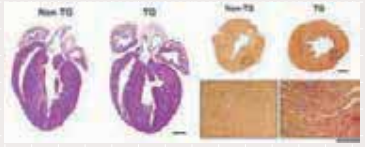


Fig. 1. Increased cardiac expression of IL-16 in mice under control of the α-MHC promoter causes increased myocardial fibrosis and stiffness. (Left) Four-chamber view of hearts from non-transgenic and transgenic mice. (Right) Sirius Red-stained sections of the LV from fibrotic areas.

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.

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) 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

(2) 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

(3) 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

(4) The apoptotic initiator caspase-8: Its functional ubiquity and genetic diversity during animal evolution. Sakamaki K., et al. ***Mol Biol Evol.*** (2014) 31 (22):3282-301

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.

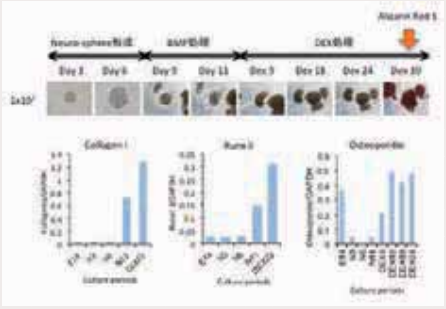


Fig. Neuro-spheres derived from ES cells are induced to undergo osteogenesis by treatment with BMP4 and DEX. Calcium deposition is shown by red-staining of alizarin, and upregulation of osteogenic marker genes during osteogenesis is detected by semi-quantitative RT-PCR.

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.

SA Prof.
Shigeyuki Hamada

SA Associate prof.
Kazuhisa Okada

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 Postdoctoral 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.

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.

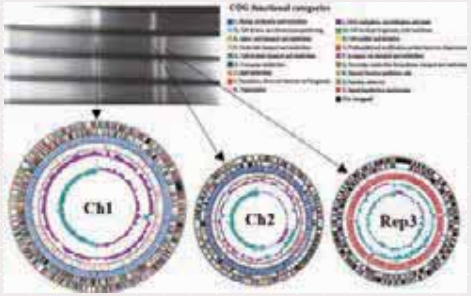


Fig. Pulsed-field gel electrophoresis of intact genomic DNA of *Vibrio cholerae* isolates and circular representation of the genome of *V. cholerae* O1 El Tor TSY216, consisting of 3 chromosomes (Emerg Infect Dis, 2015).

Thailand-Japan Research Collaboration Center

Section of Viral Infections

SA Prof.
Masashi Tatsumi

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.

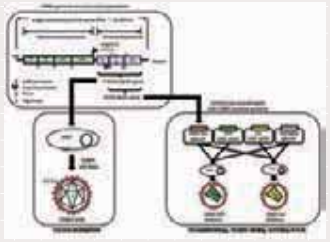


Fig. Upon expression, CHIKV (BSL3) structural proteins self-assemble into virus-like particles that are morphologically and antigenically similar to those of native CHIKV. A lentivirus pseudotyped with CHIKV envelope proteins (BSL2) was also used in the CHIKV neutralization test.

Section of Bacterial Drug Resistance Research

Thailand-Japan Research Collaboration Center

SA Prof.
Shigeyuki Hamada

Profile

Dr. Hamada received is Ph.D. from Osaka university Graduate School of Dentistry in1971. 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 a 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) Fetal septic meningitis in child caused by Streptococcus suis serotype 24. Kerdsin, A., et al. ***Emerg. Infect. Dis.*** (2016) 22(8):1519-20.

(2) Molecular and genomic characterization of pathogenic traits of group A Streptococcus pyogenes. Hamada S., et al. ***Proc. Jpn Acad. Sci.*** (2015) B91:539-59.

(3) Characterization of 3 megabase-sized circular replicons from *Vibrio cholerae*. Okada K., et al. ***Emerg. Infect. Dis.*** (2015) 21(7):1262-3.

Carbapenem-resistant Enterobacteriaceae (CRE), including *Klebsiella pneumonia* 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 Southeast Asian countries.

Carbapenem resistance is usually carried by a plasmid(s) that harbors genes encoding carbapenemases, i.e., class A KPCs, class B metallo-β-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 assigned to particular species by biochemical characterization or MALDI-TOF-MS, followed by profiling using pulse-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 infections spread and may be able to identify potential reservoirs.

Whole genome sequence data and epidemiological studies may contribute to the development of diagnostic tools and improved public health services.

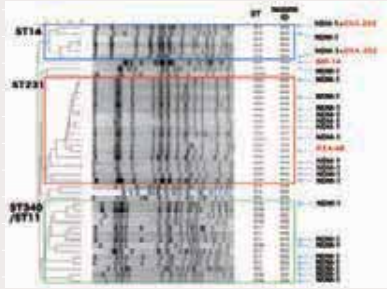


Fig. PFGE and phylogenetic relationships among 44 isolates of carbapenem-resistant *Klebsiella pneumoniae* obtained from a single hospital in Thailand. These isolates were separated into three major sequence types (ST), and comprised plasmid(s) carrying several carbapenem-resistant genes, including NDM-1, OXA-232, OXA-48, and IMP-14.

Thailand-Japan Research Collaboration Center

Section of Antiviral Research

Prof. Tatsuo Shioda

Profile

Dr. Shioda obtaind his B. Sc. from the University of Tokyo in 1982 and his Ph.D. form 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

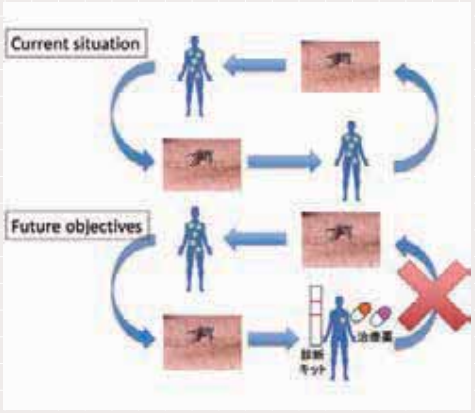
(1) Capsid-CPSF6 Interaction Is Dispensable for HIV-1 Replication in Primary Cells but Is Selected during Virus Passage In Vivo. Saito A., ***J Virol.*** (2016) 11;90 (15):6918-35.

(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.



Thailand-Japan Research Collaboration Center

Mahidol-Osaka Center for Infectious Diseases

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.

Staff

Director of MOCID: Prof. Tatsuo Shioda Ph.D
Associate Professor: Emi E. Nakayama, M.D.,Ph.D
Assistant Researcher/Ph.D student: Mr.Aekkachai Tuekprakhon B.SC.
Assistant Researcher: Juthamas Phadungsombat M.SC. (Microbiology)
Assistant Researcher: Narinee Srimark M.SC. (Public Health)

Diagnostic kit developed by the MOCID.

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.

Evaluation of CHIKV detection kit at Safdarjung Hospiral, Dehli, India

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

Endowed Chair

BIKEN Endowed Department of Dengue Vaccine Development

Endowed chair prof.
Eiji Konishi

Profile

Dr. Konishi received his Ph.D. from Kobe University in 1980. He joined Kobe University medical school and Yale University medical school after he got Ph.D. He was appointed to the current position in 2011 after working at Kobe University School of Medicine and Graduate School of Health Sciences as an Associate Professor.

Publication

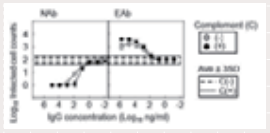
(1) A mouse monoclonal antibody against dengue virus type 1 Mochizuki strain targeting envelope protein domain II and displaying strongly neutralizing but not enhancing activity. Yamanaka A., et al. ***J Virol.*** (2013) 87(23): 12828-37.

(2) A review of successful flavivirus vaccines and the problems with those flaviviruses for which vaccines are not yet available. Ishikawa T.et al., ***Vaccine.*** (2014) 32 (12):1326-37

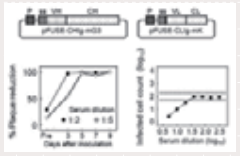
(3) Expression of enhancing-activity-free neutralizing antibody against dengue type 1 virus in plasmid-inoculated mice. Yamanaka A., et al. ***Vaccine*** (2015) Nov 9;33(45):6070-7.

The BIKEN Endowed Department of Dengue Vaccine Development was established in the Faculty of Tropical Medicine, Mahidol University, Thailand, in 2011 by an endowment from The Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan to the Research Institute for Microbial Diseases, Osaka University, Osaka, Japan. This fiscal year is the last of the 6 year contract between these organizations.

Dengue fever is a mosquito-borne viral disease that affects those living in tropical regions. However, autochthonous transmission of this disease to Japan and European countries in temperate regions was recently reported, making dengue fever a global infectious disease. An estimated 3.9 billion people are at risk of infection, with 390 million infections and 100 million cases reported annually. The recently licensed Sanofi's vaccine does not show sufficient protective efficacy. Infection-enhancing antibodies that are induced simultaneously with neutralizing antibodies may affect the activity of the latter. Thus, there is a need to design a vaccine antigen to minimize induction of infection-enhancing antibodies and, therefore, maximize vaccine efficacy. Our department has developed a new antigen that induces neutralizing, but not infection-enhancing antibodies. This technology is applicable to several vaccine strategies.



A new antigen that induces neutralizing, but not infection-enhancing, antibodies, was successfully developed using a mouse monoclonal antibody against dengue type 1 virus that possessed enhancing activity only (EAb, right panel). Manipulation of the epitope targeted by this EAb suppressed induction of EAb. We also generated a neutralizing-only antibody (NAb, left panel) and are currently analyzing its epitope, which may be relevant to the development of an effective dengue vaccine.



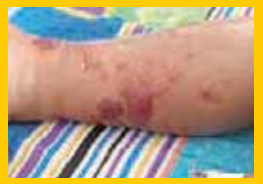
An antibody-expressing vaccine is a strategy designed to produce neutralizing-only antibodies in the host. Heavy (H)- and light (L)-chain genes encoding the antibody-binding (Fab) region of NAb were cloned into the antibody-expressing vector, pFUSE. Mice co-inoculated with two plasmids harboring the H- and L-chains produced neutralizing antibodies 3 days later (left). However, no infection-enhancing activity was detected (right). Mice maintained detectable levels of neutralizing antibodies for at least 3 months, suggesting that an antibody-expressing vaccine can be used to protect from dengue fever.

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.

<Hospitals for clinical training in Thailand>

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

BIKEN Innovative Vaccine Research Alliance Laboratories

Staff

Drector, SA Prof.
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.

Vaccine Creation Project

BIKEN Innovative Vaccine Research Alliance Laboratories

Profile

Dr. Yoshioka received his Ph.D. from Osaka University in 2004. He took his current positon 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

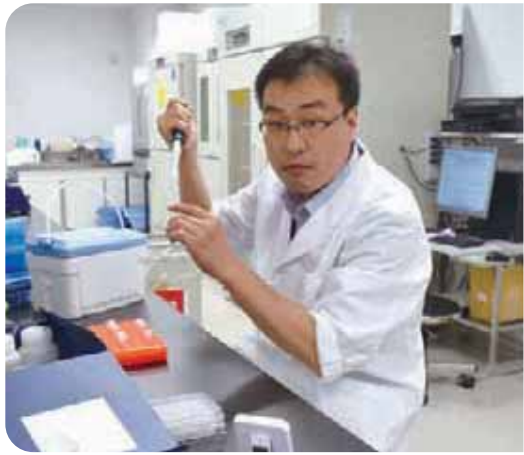
(1) Distribution of Silver Nanoparticles to Breast Milk and Their Biological Effects on Breast-Fed Offspring Mice. Morishita Y, Yoshioka Y, et al. *ACS Nano*. (2016) Aug 15.

(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 Assoc. prof.
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.

BIKEN Innovative Vaccine Research Alliance Laboratories

Mucosal Vaccine Project

SA Assoc. prof.
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) IL-10-producing CD4⁺ T cells negatively regulate fucosylation of epithelial cells in the gut. Goto Y., et al. *Sci. Rep.* (2015) 5:15918.

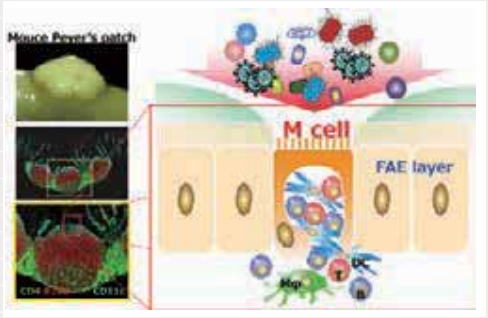
(2) Innate lymphoid cells regulate intestinal epithelial cell glycosylation. Goto Y., et al. *Science* (2014) 345 (6202):1254009.

(3) 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.

(4) Indigenous opportunistic bacteria inhabit mammalian gut-associated lymphoid tissues and share a mucosal antibody-mediated symbiosis. Obata T., et al. *Proc. Natl. Acad. Sci. U S A.* (2010) 107(16):7419-24.

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:

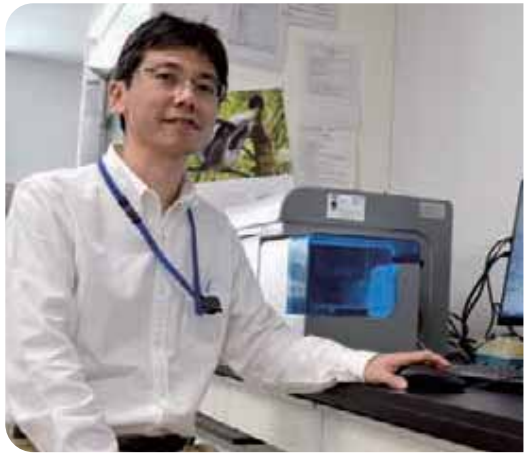
1)To identify new M cell-specific genes and elucidate the mechanism of M cell antigen uptake.
2)To understand the aged mucosal immune system and develop effective mucosal vaccines for older people.
3)To establish an *in vitro* culture system for normal and functional primary mucosal epithelial cells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



BIKEN Innovative Vaccine Research Alliance Laboratories

Vaccine Dynamics Project

SA Assoc. prof.
Taiki Aoshi



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 positon in 2015 after working at Washington University in St. Louis, NIBIOH, and IFReC 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.

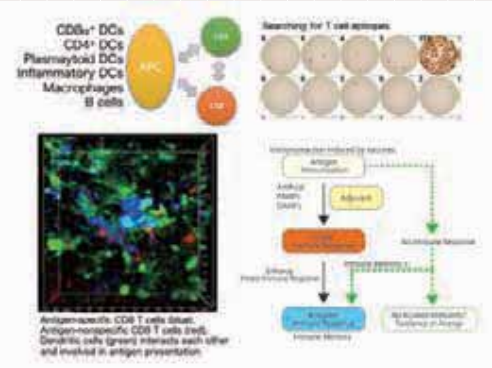
(2) Plasmacytoid dendritic cells delineate immunogenicity of influenza vaccine subtypes. Koyama S., et al. *Sci Transl Med.* (2010) Mar 31; 2(25):25ra24.

(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+ T cells. Aoshi T., et al. *Immunity* (2008) Sep 19;29(3):476-86.

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.: Masahito Ikawa, Ph.D.
Assis. prof.: Yuhkoh Satouh, Ph.D.
Assis. prof. (SUP): Yoshitaka Fujihara, Ph.D.
Assis. prof. (SUP): Haruhiko Miyata, Ph.D.
Assis. prof. (SUP): Masashi Mori, Ph.D.
SA Assis. prof. (SUP): Daiji Kiyozumi, Ph.D.
Guest Associate prof.; Ayako Isotani, 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).

DNA-chip Development Center for Infectious Diseases

Staff

Head, Prof. (SUP): Hiroshi Nojima, Ph.D.
Assoc. prof. (SUP): Norikazu Yabuta, Ph.D.
Assis. prof.: Daisuke Okuzaki, Ph.D.

Facility Management: The DNA-chip Development Center for Infectious Diseases is a unique facility that was established in 2004 to analyze the transcriptional dynamics and variations involved in infectious diseases. We provide the following contract analysis services and various research supports such as use briefings and training courses of installed apparatus. We also conduct the following research projects in this facility.

(A) Contract analysis service

(1) Transcriptome analysis using DNA-chip analyzers.
The high density DNA microarray system in this facility permits comprehensive transcriptional analysis of gene expression in the human or mouse host, and in various pathogenic organisms. Two DNA microarray systems, namely the Agilent-type and the Affymetrix-type, are available in this center.

(2) Nano-counter Analysis System (NanoString Technologies):
This system is also useful for more accurate quantitative analysis of the transcriptional levels of particular genes.

(3) Proteome analysis using mass spectrometry.
The MS/MS spectrometer installed in this facility enables the analysis of the expression, interactions and modifications of proteins from humans, mice, and pathogenic organisms. This center is also capable of recent technical innovations, such as the mass spectrometric detection of pathogenic organisms that facilitates the development of novel diagnostic systems for infectious diseases.

(4)Gene expression analysis using Next Generation Sequencer (collaboration with Dept of Infection Metagenomics)

(5) Gene data analysis.
Gene data analysis using IPA and NextBio is also available in this center.

(B) Research Projects

Based on DNA microarray analysis on mRNA from the peripheral blood mononuclear cell (PBMC) of patients suffered from autoimmune diseases such as vasculitis, we have identified several genes that are specifically up-regulated in PBMC of these patients. IPA and NextBio softwares we used are useful data mining tools to detect such disease specific genes from big data obtained comprehensive gene analysis without deep knowledge on bioinformatics.

Publication

(1) IFI27 Is a Useful Genetic Marker for Diagnosis of Immunoglobulin A Nephropathy and Membranous Nephropathy Using Peripheral Blood. Nagasawa Y., et al. ***PLoS One.*** 2016 Apr 21;11(4):e0153252.

(2)Interleukin-18-deficient mice develop dyslipidemia resulting in nonalcoholic fatty liver disease and steatohepatitis. Yamanishi K., et al. ***Transl Res.*** 2016 Mar 19.

(3) Microarray and whole-exome sequencing analysis of familial Behçet's disease patients. Okuzaki D., et al. ***Sci Rep.*** 2016 Jan 20;6:19456. doi: 10.1038/srep19456.

(4) CAWS administration increases the expression of interferon gamma and complement factors that lead to severe vasculitis in DBA/2 mice. Nagi-Miura N., et al. ***BMC Immunol.*** 2013 Sep 24;14(1):44.

DNA microarray

nCounterSystem

Next Generation Sequencer HiSeq

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.

Research Promotion Group

Associate Professor:
Yoshiko Murakami,
M.D., Ph.D.

Our aim is to promote collaborative research, information exchange, and people-to-people exchange between laboratories via:

1. **Organization of the Awaji International Forum on Infection and Immunity (annually in September). http://awaji-forum.com**
2. **Organization of the Biken monthly seminar for reporting research progress.**
3. **Organization of the Annual Research presentation program and the competition of research presentations.**

Awaji International Forum

Awaji Yumebutai
International Conference Center

A seminar held in December

Academic Prize awardee

Research projects

Dr. Murakami concurrently serves as the leader of the PNH group in the Dept. of Immunoregulation and undertake the following profects.

1. **Investigation of the pathogenesis of acquired glycosylphosphatidylinositol (GPI) deficiency and PNH.**
2. **Investigation of the pathogenesis of IGD.**

See the Dept. of Immunoregulation and website (http://igd.biken.osaka-u.ac.jp) for details.

Publication

(1) Pathogenic variants in PIGG cause intellectual disability with seizures and hypotonia. Makrythanasis P, et al. ***Am. J. Hum. Genet.*** (2016) 98:615-26.

(2) 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.

(3) 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) 51:203-7.

Education Promotion Group

Associate Professor:
Hodaka Fujii,
M.D., Ph.D.

Assistant Professor:
Toshitsugu Fujita,
Ph.D.

To facilitate research on microbiology and immunology, we have based our multidisciplinary graduate program on microbiology and immunology. We dedicate to planning and management of the graduate program and also organize Open House sessions and provide guidance for new graduate students and post-docs. The aim of these activities is to promote communication between researchers and to develop human resources with expertise covering both microbiology and immunology.

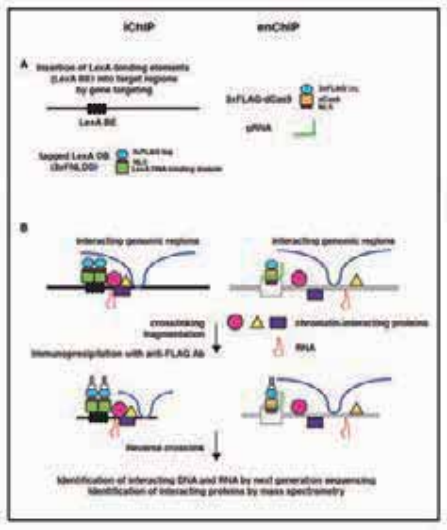
Lecture series for graduate students

Joint Orientation for RIMD and IFReC

Research Project
(Chromatin Biochemistry Research Group)

Biochemical analysis of molecular mechanisms of genome functions using the locus-specific chromatin immunoprecipitation technologies

A comprehensive understanding of the mechanisms underlying genome function, such as transcription and epigenetic regulation, requires identification of molecules that bind to the genomic regions of interest *in vivo*. To facilitate the biochemical and molecular biological analysis of specific genomic regions, we have developed locus-specific chromatin immunoprecipitation technologies (iChIP and enChIP) to purify the genomic regions of interest. We will then apply these locus-specific ChIP methods to elucidate the molecular mechanisms underlying important epigenetic phenomena such as regulation of tumor suppressor gene expression, DNA repair, and the lineage commitment of lymphocytes.



Publication

(1) Efficient sequence-specific isolation of DNA fragments and chromatin by in vitro enChIP technology using recombinant CRISPR ribonucleoproteins. Fujita T., et al. ***Genes Cells*** (2016) 21:370-7.

(2) Identification of non-coding RNAs associated with telomeres using a combination of enChIP and RNA sequencing. Fujita T., et al. ***PLoS One*** (2015) 10:e0123387.

(3) Identification of proteins associated with an IFNγ-responsive promoter by a retroviral expression system for enChIP using CRISPR. Fujita T., et al. ***PLoS One*** (2014) 9: e103084.

Common Research Facilities

Central Instrumentation Laboratory

Head, Professor:
Hiroaki Miki, Ph.D.
Associate professor:
Shinji Higashiyama, Ph.D.
Associate professor:
Naohisa Goto, Ph.D.
Assistant professor:
Kazunobu Saito, Ph.D.
SA Assistant professor:
Miki Morimatsu, 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

Radioisotope Labolatory

Head, Professor:
Hiroaki Miki, Ph.D.
Associate professor:
Shinji Higashiyama, 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 stockroom, 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.

Common Research Facilities

Central Laboratory for Biological Hazardous Microbes

Head, Professor:
Tatsuo Shioda, Ph.D.

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^2 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.

RIMD library

Head, Professor:
Tetsuya Iida, Ph.D.

The RIMD library contains academic books and journals about microbiology, immunology, oncology, and other related scientific fields such as cell biology, genetics, histology, developmental biology, biochemistry, pharmacology, and pathology. In particular, we have collected rare books on parasitology that cannot be found at other institutions; these books are frequently accessed by visitors to the RIMD library. Now, the RIMD library owns 6,800 books and dozens of scientific journals, some of which are donated by the BIKEN foundation. Most of the books and journals in the RIMD library are registered on the index at the main Library of Osaka University, which can also be accessed by libraries throughout Japan via the Interlibrary Loan (ILL) system. One librarian handles the RIMD library, and two professors and two associate professors are members of the RIMD library committee.

Administration and Research Support

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

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.

1930

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).

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.

1940

1950

Discovered *Vibrio parahaemolyticus*

Tsunesaburo Fujino

1960

Discovered cell fusion

Yoshio Okada

Developed a measles vaccine

Yoshiomi Okuno

1967

RIMD moved to the Suita Campus

RIMD buildings in 1967

1970

Discovered a viral oncogene

Kumao Toyoshima

1980

Developed a chickenpox vaccine

Michiaki Takahashi

1990

Elucidation of the Innate Immune System

Shizuo Akira

2000

Approved as a Joint Usage/Research Center by MEXT

2010

Developed a malaria vaccine

Toshihiro Horii

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.

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

Koch's microscope

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 2015-16

Presentation Award (1st Prize), The 16th Kansai Glycoscience Forum	
Tetsuya Hirata Department of Immunoregulation	2015.5.16
DGD Wiley Blackwell Prize 2015	
Daisuke Mashiko Department of Experimental Genome Research	2015.6.4
Young Scientist Award for Best Presentation, The 67th Annual Meeting of the Japan Society for Cell Biology	
Hiroyasu Kidoya Department of Signal Transduction	2015.7.1
Best Presentation Award, The 36th Annual Meeting of the Japanese Society of Inflammation and Regeneration	
Hiroyasu Kidoya Department of Signal Transduction	2015.7.21
Presentation Award, The 52nd Japanese Complement Symposium	
Yoshiko Murakami Department of Immunoregulation	2015.8.21
Presentation Award, The 10th Vascular Biology Innovation Conference	
Hiroyasu Kidoya Department of Signal Transduction	2015.8.23
Best Abstract Award, The 6th Molecular Cardiovascular Conference II	
Hiroyasu Kidoya Department of Signal Transduction	2015.9.5
International Glycoconjugate Organization (IGO) Award 2015	
Taroh Kinoshita Department of Immunoregulation	2015.9.15
Poster Presentation Award, The 43rd Annual Meeting of the Japan Society for Clinical Immunology	
Ryosuke Hiwa Department of Immunochemistry	2015.10.23
Encouraging Prize for Young Scientisits, The 9th Wakate Colosseum for Bacteriology	
Keiji Nakamura Department of Molecular Bacteriology	2015.11.25
Encouraging Prize for Young Scientisits, The 9th Wakate Colosseum for Bacteriology	
Keisuke Ishigaki Department of Molecular Bacteriology	2015.11.25
Encouraging Prize for Young Scientisits, The 68th Japanese Society for Bacteriology, in Kansai Region	
Sayaka Nishikawa Department of Molecular Bacteriology	2015.11.28
Encouraging Prize for Young Scientisits, The 68th Japanese Society for Bacteriology, in Kansai Region	
Keisuke Ishigaki Department of Molecular Bacteriology	2015.11.28
Ursula and Fritz Melchers Travel Award	
Ryosuke Hiwa Department of Immunochemistry	2015.12.1
Best Presentation Award for Young Scientists, BMB2015	
Satomi Mukai Department of Molecular Genetics	2015.12.4
Best Presentation Award for Young Scientists, BMB2015	
Gun-hee Lee Department of Immunoregulation	2015.12.4
Awards of Excellence, The Japanese Vascular Bilology and Medicine Organization	
Daishi Yamakawa Department of Signal Transduction	2016.3.5
Best Poster Presentation Award, The 5th Cell Competition Colloquium	
Hiroya Ohkura Department of Oncogene Research	2016.3.17
Presentation Award, The 89th Annual Meeting of Japanese Society for Bacteriology	
Keisuke Ishigaki Department of Molecular Bacteriology	2016.3.23

Hiroyasu Kidoya
Best Presentation Award
36th JSIR

Daishi Yamakawa
Awards of Excellence
JVBM

Taroh Kinoshita
IGO Award 2015

Yoshiko Murakami
Presentation Award
52nd JCS

Highly cited researchers 2015

Shizuo Akira
Department of
Host Defense

Masahiro Yamamoto
Department of
Immunoparasitology

Shintaro Sato
Mucosal Vaccine Project,
BIKEN Innovative Vaccine Research
Alliance Laboratories

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, Short term	Specific Research project, Short term	Research project, Long term	To help victims of 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
Total	109	44	52	4	209

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 Infection and Immunity 	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 and IFReC conducts world-class researches in biological fields includingthe 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 translateing the research achievements in of RIMD and IFReC to the whole of society. In addition, the foundation is dedicated to promotinge basic research by through the Taniguchi Memorial Scholarship program and the BIKEN Center for Innovative Vaccine Research Alliance LabsLaboratories.

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

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

> 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 provides our own scholarships for international students, Taniguchi scholarship. 3 grad students from Indonesia (2 students in master's course, 1 student in doctoral course) are studying in RIMD on this scholarship.

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 (2016.4)

Staffs

Professor	16
Endowed Chair Professor	1
SA Professor	4
Associate Professor	17
SA Associate Professor	11
Assistant Professor	26
Endowed Chair Assistant Professor	1
SA Assistant Professor	5
Educational Support Staff	3
Technical Staff	15
Adniministrative Staff	20
SA Researcher	37
Part-time General & Technical Staff	42
Total	198

(SA: Specially Appointed)

Graduate Students

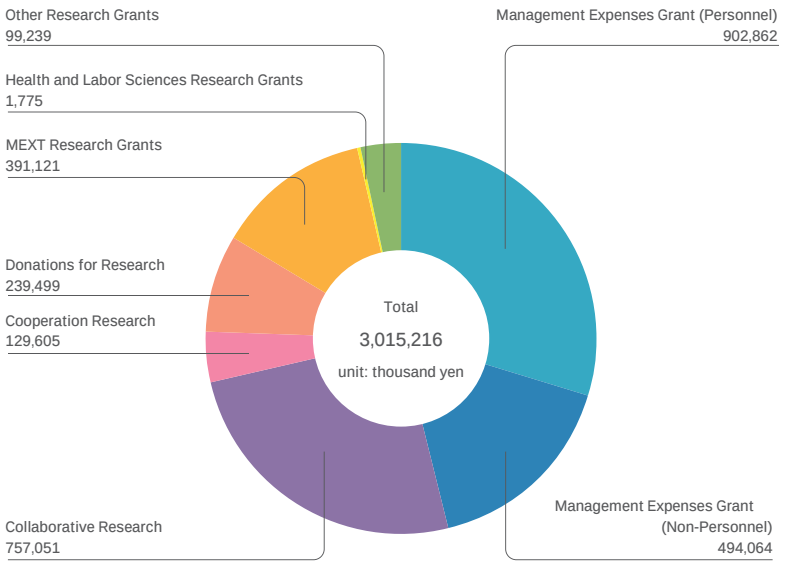
	①	②
Graduate school of Medicine	43	6
Graduate school of Science	4	9
Graduate school of Pharmaceutical Science	4	0
Graduate school of Dentistry	2	0
Graduate school of Frontier Biosciences	19	0

①Doctoral Program
②Master' s Program

Research Fellows and Research Students

Special research students	2
Research students	3
JSPS Research fellows	13

ACCOUNTS



BUILDING AREA

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

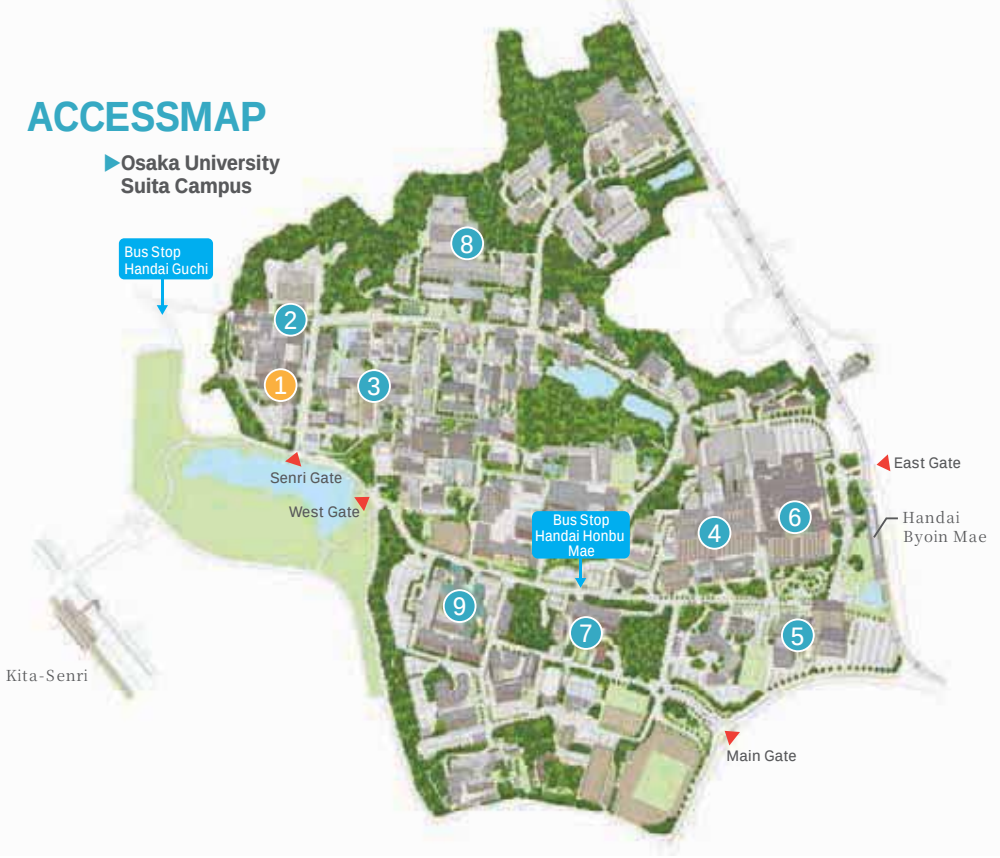
② South Building

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

ACCESSMAP



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