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Osaka University RIMD Research Institute for Microbial Diseases 2021-2022

2021-2022

RESEARCH INSTITUTE FOR MICROBIAL DISEASES

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

RIMD
Research Institute for Microbial Diseases
大阪大学微生物病研究所

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 spatiotemporal 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.

Director
Research Institute for Microbial Diseases
Osaka University

Masato Okada

CONTENTS

ORGANIZATION

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

RIMD
Research Institute for Microbial Diseases
大阪大学微生物病研究所

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 — Watanabe Lab
- Dept. of Immunoparasitology — Yamamoto Lab
- Dept. of Infection Microbiology — Mimuro Lab
- Institute for Advanced Co-Creation Studies — Okamoto Lab

To explore the mechanisms that protect against microbes

DIVISION OF HOST DEFENSE

- Dept. of Molecular Immunology — Yamasaki Lab
- Dept. of Host Defense — Akira Lab
- Dept. of Immunochemistry — Arase Lab
- Dept. of Immune Response Dynamics — Suzuki Lab

To explore regulatory mechanisms in cancer cells

DIVISION OF CELLULAR AND MOLECULAR BIOLOGY

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

COMMON RESEARCH FACILITIES

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

ADMINISTRATION

- General Affairs Section / Accounting Section Research Cooperation Section

OFFICE FOR RESEARCH PROMOTION

Special Research Facilities

To overcome infectious diseases

RESEARCH CENTER FOR INFECTIOUS DISEASE CONTROL

- Dept. of Bacterial Infections — Iida Lab
- Dept. of Molecular Protozoology — Iwanaga Lab
- Dept. of Virology — Kobayashi Lab
- Laboratory of Virus Control — Matsuura Lab

To understand our body system from genetic information

GENOME INFORMATION RESEARCH CENTER

- Dept. of Experimental Genome Research — Ikawa Lab
- Dept. of Genome Informatics — Daron Lab
- Dept. of Infection Metagenomics — Iida Lab
- NGS Core Facility
- Network Administration Office

To develop new therapeutic approaches to infectious diseases

INTERNATIONAL RESEARCH CENTER FOR INFECTIOUS DISEASES

- Laboratory of Emerging Viral Diseases — Iwasaki Lab
- Laboratory of Pathogen Detection and Identification — Nakamura Lab
- Laboratory of Viral Dynamism Research — Maeda Lab
- Laboratory of Clinical Research on Infectious Diseases — Kamitani Lab
- Pathogenic Microbes Repository Unit

ANIMAL RESOURCE CENTER FOR INFECTIOUS DISEASES

RESEARCH CENTER FOR MECHANISM AND REGULATION OF AGING

- Division of Aging Model Organism
- Division of Cellular Senescence

THAILAND-JAPAN RESEARCH COLLABORATION CENTER

- Section of Bacterial Infections
- Section of Viral Infections
- Section of Bacterial Drug Resistance Research
- Section of Antiviral Research
- Mahidol-Osaka Center for Infectious Diseases

ENDOWED CHAIR

- Yabumoto Dept. of Intractable Disease Research — Kinoshita Lab
- Dept. of Malaria Vaccine Development — Horii Lab
- Dept. of Cellular Immunology — Aoshi Lab

To develop novel vaccines with high safety and efficacy

BIKEN INNOVATIVE VACCINE RESEARCH ALLIANCE LABORATORIES

- Vaccine Creation Group — Yoshioka Lab
- Virus Vaccine Group — Ebina Lab

ORGANIZATION

Research Institute for Microbial Diseases

DEPT. 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.

Yasuhiko Horiguchi

Professor

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 positon as Postdoc in 1990, a Research Associate in 1992, an Associate Professor in 1998. He was appointed current position in 2001.

STAFF

Asst. Prof. : Yukihiro Hiramatsu ／
Asst. Prof. : Takashi Nishida ／
Grad. Student 6

Publication

(1) *Bordetella* dermonecrotic toxin is a neurotropic virulence factor that uses CaV3.1 as the cell surface receptor.Teruya S. et al. ***mBio*** (2020)11:e03146-19.

(2) Bordet - Gengou agar medium supplemented with albumin - containing biologics for cultivation of bordetellae. Hiramatsu Y. et al. ***Microbiology and Immunology*** (2019) 63 (12):513-516.

(3) BspR/BtrA, an anti-σ factor, regulates the ability of *Bordetella bronchiseptica* to cause cough in rats. Nakamura K. et al. ***mSphere*** (2019) 4:e00093-19

(4) The Eukaryotic Host Factor 14-3-3 Inactivates Adenylate Cyclase Toxins of Bordetella bronchiseptica and B. parapertussis, but not B. pertussis. Fukui-Miyazaki A.et al. ***mBio*** (2018)9(4), 49–15.

(5) Ectopic Expression of O Antigen in Bordetella pertussis by a Novel Genomic Integration System.Ishigaki K.et al. ***mSphere*** (2018). 3 (1)e00417–17–11.

(6) The bvg-repressed gene brtA, encoding biofilm-associated surface adhesin, is expressed during host infection by Bordetella bronchiseptica. Nishikawa, S.et al. ***Microbiology and Immunology*** (2016)60(2), 93–105.

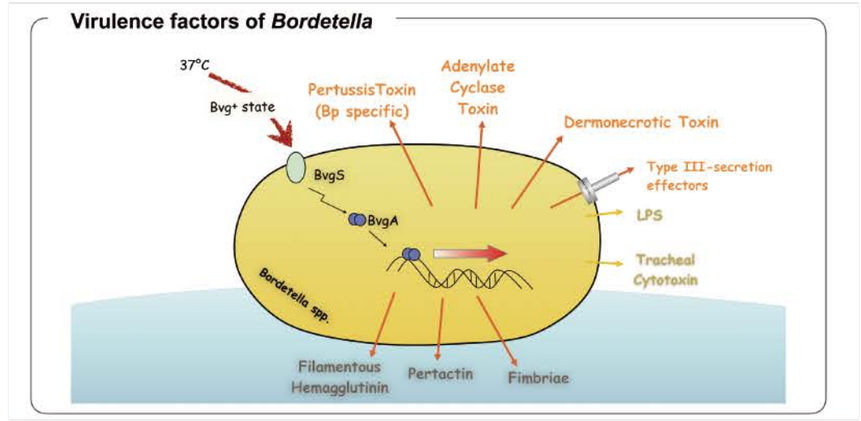
●To understand the mechanism of infection

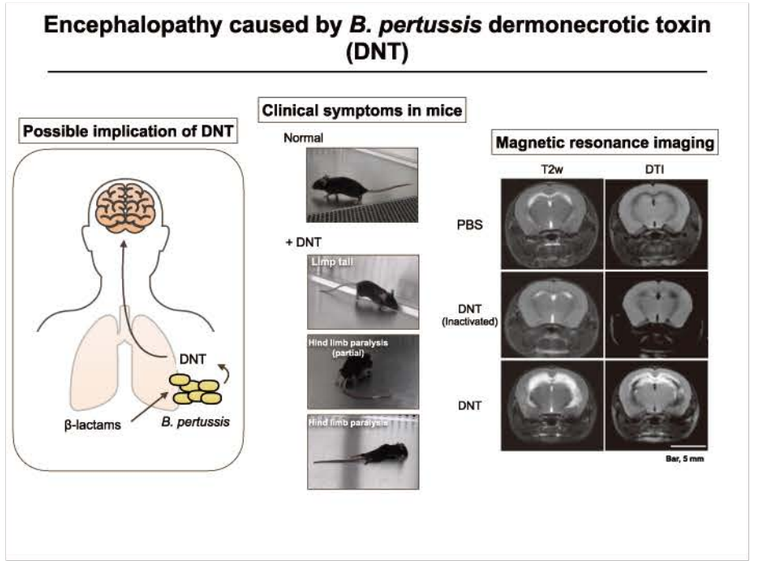
Bordetella pertussis, which is one of our research subjects is a representative pathogenic bacteria of Bordetella and causes whooping cough. In addition to B. pertussis, B. parapertussis and B. bronchiseptica are categorized in the genus Bordetella. Although these pathogenic organisms share homologous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

●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.





DEPT. OF VIRAL INFECTIONS

Although we have been studying HIV for more than 20 years, now we are mainly studying mosquito-borne viral diseases such as dengue and chikungunya virus infections. We are conducting epidemiological studies in Thailand and molecular studies in Osaka, Japan.

Tatsuo Shioda

Professor

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.

STAFF

Assoc. Prof. : Emi E. Nakayama ／
Asst. Prof. : Tadahiro Sasaki ／
Undergrad. Student 1 ／ Grad. Student 1 ／
Research Student 1

Publication

(1) Emergence of genotype Cosmopolitan of dengue virus type 2 and genotype III of dengue virus type 3 in Thailand. Phadungsombat J et al. ***PLoS One.*** (2018) 13 (11):e0207220. doi: 10.1371/journal.pone.0207220

(2) HIV-1 is more dependent on the K182 capsid residue than HIV-2 for interactions with CPSF6.Saito A. et al., ***Virology*** (2019) 532:118-126.

(3) Genotype replacement of dengue virus type 3 and lineage replacement of dengue virus type 2 genotype Cosmopolitan in Dhaka, Bangladesh 2017. Suzuki K., et al. ***Infect Genet Evol.*** (2019) 75:103977

(4) Multiple pathways to avoid IFN-β sensitivity of HIV-1 by mutations in capsid. Sultana T., et al., ***J Virol.*** (2019) 93(23).

(5) Two distinct lineages of chikungunya virus cocirculated in Aruba during the 2014–2015 epidemic. Phadungsombat J., et al. ***Infect Genet Evol.*** (2020) 78:104129

(6) The 4th and 112th residues of viral capsid cooperatively modulate capsid-CPSF6 interactions of HIV-1. Saito A., et al.. ***AIDS Res Hum Retroviruses*** (2020) doi:10.1089/AID.2019.0250.

●Molecular characterization of dengue and chikungunya viruses

Dengue and chikungunya viruses are transmitted by Aedes mosquitos and cause febrile diseases. Dengue virus sometimes causes shock syndrome after decline of fever and chikungunya virus causes arthralgia. We are conducting molecular epidemiology of these viruses in Thailand and Bangladesh by using molecular clock analysis. There are apparent variations in growth kinetics among isolated viruses and we are trying to elucidate factors affecting these differences.

●Characterization of anti-dengue antibodies

Anti-dengue antibodies show both neutralizing and enhancing effect on virus infection. We are analyzing several monoclonal antibodies hoping to find neutralizing antibody without any enhancing effect. There are four serotypes of dengue virus. Some antibodies neutralize all four serotypes while other potently neutralize only one serotype. Antibodies with strong neutralizing activity without any enhancement can be used as antibody drug. We will also analyze anti-viral antibodies in asymptomatic infection.

●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.

Fig. 1.Phylogeographical analysis of dengue virus type 2.

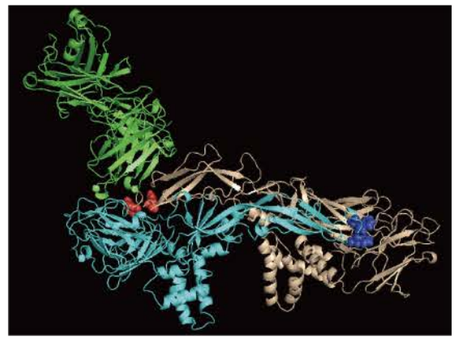


Fig. 2.A neutralizing antibody (green) and envelope dimer of dengue virus type 2 (pale blue and orange). Amino acid resides critical for antibody binding are highlighted with red and blue.

DEPT. OF MOLECULAR VIROLOGY

A virus is a simple and very tiny structure composed of protein shells and nucleic acids. It is surprising that such a small entity can sometimes cause pandemics, resulting in significant global damage. In our laboratory, we focus on viruses that cause zoonotic diseases, such as influenza, COVID-19, and Ebola, and elucidate the mechanisms of host adaptation, replication, and pathogenicity of viruses. We also aim to develop safe and effective vaccines by utilizing the knowledge obtained from our fundamental research.

Tokiko Watanabe

Professor

Dr. Watanabe received her PhD from Hokkaido University in 2002. She worked as a postdoctoral fellow (2002) and staff scientist (2006) at the University of Wisconsin-Madison in the USA, and as a group leader of the ERATO Kawaoka Infection-induced Host Responses Project in 2010. From there she moved on to act as a project associate professor (2013) in the Institute of Medical Science at the University of Tokyo and was appointed to her current position in 2020.

STAFF

Asst. Prof. : Shintaro Shichinohe ／ Asst. Prof. : Itsuki Anzai ／ Postdoc. : Kosuke Takada

Publication

(1) Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Imai M., et al. ***Proc Natl Acad Sci USA.*** 2020, 117(28):16587-16595.

(2) Villains or heroes? The raison d'tre of viruses. Watanabe T, Kawaoka Y. ***Clin Transl Immunology.*** 2020, 9(2):e01114.

(3) A Highly Pathogenic Avian H7N9 Influenza Virus Isolated from A Human Is Lethal in Some Ferrets Infected via Respiratory Droplets. Imai M, Watanabe T, Kiso M et al. ***Cell Host Microbe.*** 2017, 22(5):615-626.e8.

(4) Influenza virus-host interactome screen as a platform for antiviral drug development. Watanabe T., et al. ***Cell Host Microbe.*** 16: 795-805. 2014.

(5) Circulating avian influenza viruses closely related to the 1918 virus have pandemic potential. Watanabe T, Zhong G, Russell CA et al. ***Cell Host Microbe.*** 15: 692-705. 2014.

(6) Characterization of H7N9 influenza A viruses isolated from humans. Watanabe T., et al. ***Nature.*** 501:551-5. 2013.

●Research on emerging zoonotic viruses

The development of modern medicine has allowed us to eliminate numerous infectious diseases; however, humans constantly face threats from novel infectious diseases that were previously unrecognized. These so-called emerging infectious diseases are caused by newly identified species or strains; for example, Ebola, AIDS, SARS, avian influenza, and MERS which have all appeared in human society over the last several decades. More recently, SARS-CoV-2 emerged in China at the end of 2019 and spread across the world, causing the COVID-19 pandemic. Most emerging infectious diseases are zoonotic and are caused by viruses that originate in wild animals. To cause zoonosis, the pathogens that originate in animals must cross the species barrier and transmit to humans. If these pathogens are able to efficiently transmit from human to human, a pandemic is likely to emerge and threaten the lives of humans around the world.

Influenza A viruses, one of the most important zoonotic viruses, cause annual epidemics and recurring pandemics. In addition, recent sporadic human infections with avian influenza viruses have raised concerns regarding the pandemic potential of these viruses. Although influenza A viruses can infect a wide range of species, host restriction usually constrains their interspecies transmission; however, mammalian-adaptive mutations have been identified in some viral proteins that allow avian influenza viruses to overcome the species barrier.

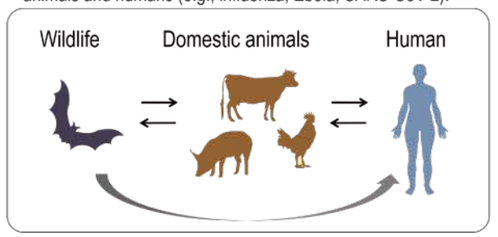
In our laboratory, we aim to elucidate the mechanisms of viral replication, pathogenicity, and the viral strategy to adapt mammalian hosts for influenza viruses. Further, we have been working with collaborators in Sierra Leone in West Africa and Brazil in South America to understand the epidemic of various zoonotic viruses in wild animals.

●Development of safe and effective vaccines for viral diseases

The current inactivated influenza vaccine has low immunogenicity. The use of adjuvants has been considered to enhance the vaccine effect, but there are still concerns about the safety of unwanted side effects. Given this and our desire to develop a safe and effective influenza vaccine, we are trying to find novel adjuvant candidates with superior safety and a robust immunostimulatory effect. In addition to influenza vaccines, we have also conducted research related to the development of vaccines against COVID-19 and Ebola virus disease.

Emerging zoonoses

Infectious diseases that can be naturally transmitted between animals and humans (e.g., influenza, Ebola, SARS-CoV-2).



❖ A significant threat to global public health

Department of Molecular Virology

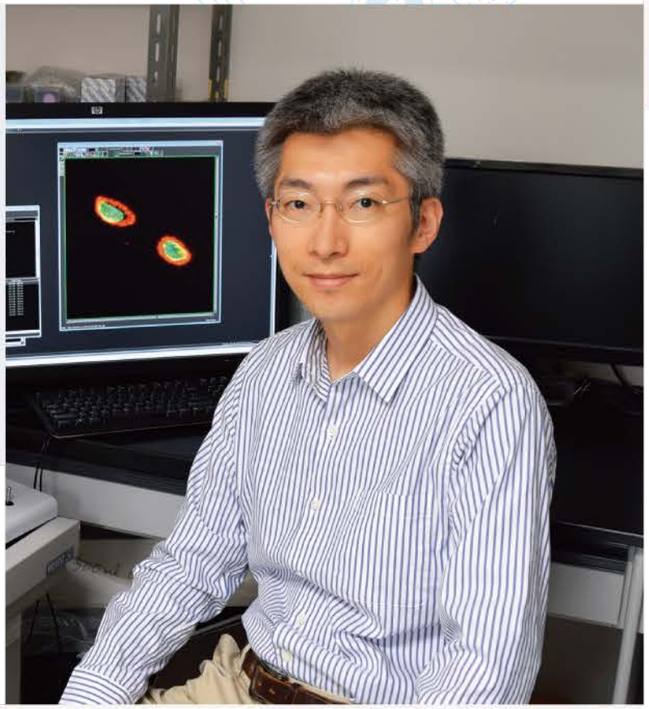
❖Research on emerging zoonotic viruses

- The mechanisms of viral replication and pathogenicity of influenza viruses
- Characterization of SARS-CoV-2
- Development of safe and effective vaccines for viral diseases
- Exploration of various viruses in wild animals

Control of emerging zoonotic viral diseases

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.



Masahiro Yamamoto

Professor

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.

STAFF

Assoc. Prof. : Miwa Sasai ／
Postdoc. : Masaaki Okamoto ／
Grad. Student 4

Publication

(1) Uncovering a novel role of PLCβ4 in selectively mediating TCR signaling in CD8+ but not CD4+ T cells. Sasai M., et al. ***J Exp Med.*** (2021) In press.

(2) CXCR4 regulates Plasmodium development in mouse and human hepatocytes. Bando H., et al., ***J Exp Med.*** (2019) 216:1733-1748.

(3) Essential role for GABARAP autophagy proteins in interferon-inducible GTPase-mediated host defense. Sasai M., et al., ***Nat Immunol.*** (2017) 18(8):899-910.

(4) 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.

(5) 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.

(6) 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.

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 inanti-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.

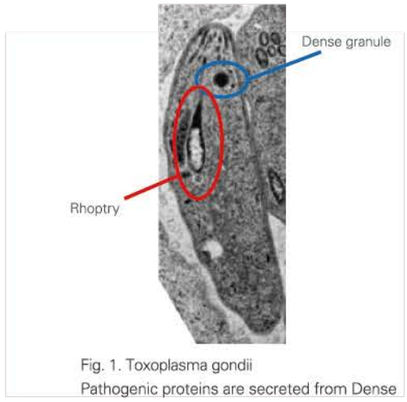


Fig. 1. Toxoplasma gondii
Pathogenic proteins are secreted from Dense granules and Rhoptry.

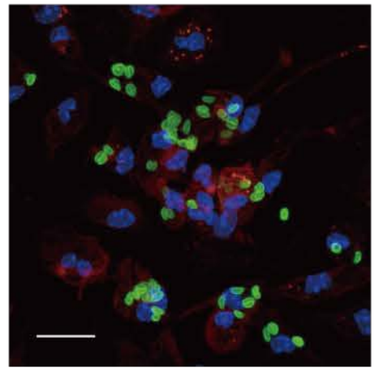


Fig. 2. Toxoplasma gondii (green) proliferating inside macrophages (red).

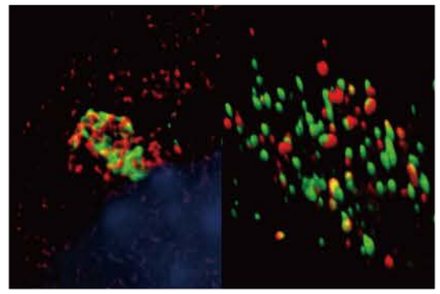


Fig. 3. Gate-16 (red) is required for antimicrobial host defense through cytosolic distribution of GTPase (green).
GTPase punctae are colocalized with Gate-16 (right fig.) throughout the cell. However, expression of mutant Gate-16 leads to GTPase aggregation and hampers immune response against pathogens.

DEPT. OF INFECTION MICROBIOLOGY

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

Hitomi Mimuro

Associate professor

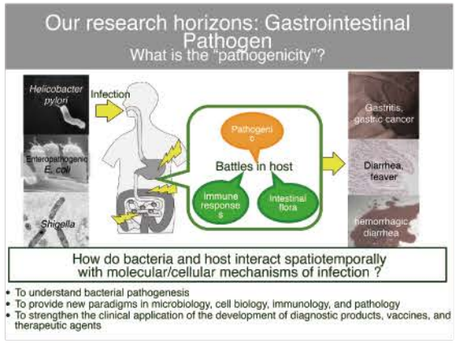
Dr. Mimuro received her Ph.D. from The University of Tokyo in 2004. She became Assistant professor at the Institute of Medical Science, The University of Tokyo in 2005 and worked for the same institution. She was appointed Associate Professor in RIMD in 2017.

STAFF

Asst. Prof. : Ryo Kinoshita-Daitoku ／
Grad. Student 3

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

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



Publication

(1) A bacterial small RNA regulates the adaptation of Helicobacter pylori to the host environment. Kinoshita-Daitoku R., et al. ***Nature Commun.*** (2021) 12(1):2085

(2) Mutational diversity in mutY deficient Helicobacter pylori and its effect on adaptation to the gastric environment. Kinoshita-Daitoku R., et al. ***Biochem Biophys Res Commun.*** (2020) 525 (3):806-811

(3) Group A Streptococcus establishes pharynx infection by degrading the deoxyribonucleic acid of neutrophil extracellular traps. Tanaka M., et al. ***Sci Rep.*** (2020)10(1):3251

(4) Shigella effector IpaH4.5 targets 19S regulatory particle subunit RPN13 in the 26S proteasome to dampen cytotoxic T lymphocyte activation. Otsubo R., et al. ***Cell Microbiol.*** (2019) 21(3):e12974.

INST. FOR ADVANCED CO-CREATION STUDIES

Our research is focusing on pathogenesis of infection with hepatitis viruses such as Hepatitis C virus and Hepatitis B virus and with mosquito-borne flaviviruses such as Japanese encephalitis virus (JEV), Dengue virus (DENV) and Zika virus (ZIKV). It still remains unclear how these viruses induce a variety of diseases in hosts. We aim to study to understand molecular mechanisms of pathogenicity of virus infection through molecular biology and animal models.

Toru Okamoto

Professor

Dr. Okamoto received his Ph.D. from Osaka University in 2006. Thereafter he worked as a postdoctoral fellow at RIMD in 2006, a researcher at Walter and Eliza Hall Institute of Medical Research in 2008. He was appointed as a current position from 2019 after working as an assistant professor (2012) and an associate professor (2017) at Research Institute for Microbial Diseases.

Publication

(1) Novel anti-flavivirus drugs targeting the nucleolar distribution of core protein.Tokunaga M., et al. ***Virology*** 2019 541:41-51

(2)Infection with flaviviruses requires BCLXL for cell survival. Suzuki T. & Okamoto T., et al. ***PLoS Pathog.*** 2018 Sep 27; 14 (9):e1007299.

(3)Characterization of SPP inhibitors suppressing propagation of HCV and protozoa. Hirano J. & Okamoto T., et al. ***Proc Natl Acad Sci U S A.*** 2017 Dec 12;114 (50):E10782-E10791.

(4)TRC8-dependent degradation of hepatitis C virus immature core protein regulates viral propagation and pathogenesis. Aizawa S. & Okamoto T., et al. ***Nat. Commun.*** 2016 May 6; 12(5): e1005610

STAFF

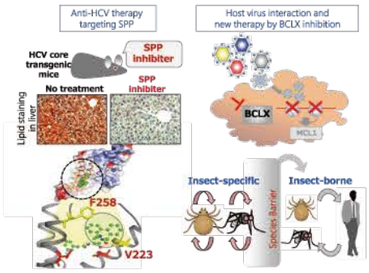
Asst. Prof. : Tatsuya Suzuki ／ Postdoc. : Yumi Ito

●Pathogenicity of hepatitis viruses

Infection with Hepatitis C virus (HCV) induces chronic infection and leads to develop steatosis, cirrhosis and hepatocellular carcinoma. Among 10 viral proteins, HCV core protein forms a viral particle and induces steatosis and hepatocellular carcinoma in transgenic mice model. It suggests that core is strongly associated with liver diseases in chronic hepatitis C. Our research is focusing on maturation of core protein by signal peptide peptidase (SPP) and its maturation is essential for formation of viral particle and development of liver diseases. We would like to clarify why maturation of HCV core is needed for its function, especially liver diseases.

●Pathology of mosquito-borne flavivirus and development of new antiviral drugs

Infectious diseases by infection with mosquito-borne flavivirus, one of which is microcephaly by infection with Zika virus, have become a serious problem worldwide. Mosquito-borne flavivirus spreads infection through blood feeding of virus-infected mosquito. While host ranges of virus infection are generally limited, mosquito-borne flavivirus can propagate mosquito and mammals. We study how mosquito-borne flavivirus infects mosquito and mammals and how transmission between mosquito and mammals is associate to development of diseases.



DEPT. OF MOLECULAR IMMUNOLOGY

Our bodies are continuously exposed to external and internal insults caused by infection and tissue damage, most of which are primarily sensed by immune receptors to maintain tissue homeostasis. However, the molecular mechanism by which these receptors discriminate diverse insults to elicit suitable immune responses remains elusive. We have found that C-type lectin receptors can sense both damaged self and non-self pathogens (Figure 1). Recently, we also showed that clustered C-type lectin receptors, Mincle, MCL, Dectin-2 and DCAR, can recognize mycobacteria through their unique glycolipids possessing adjuvant activity (Figure 2). Our objective is to illustrate the principle behind the regulation of immune responses through C-type lectin receptors in physiological and pathological settings. Based on these results, we also aim to design new methods to efficiently elicit or modulate immune responses.
To this end, our research is focusing on the following axes:
1) Immune sensing of pathogens and damaged-self via C-type lectin receptors.
2) Unique T cell responses induced by self peptides.
3) Atypical T cell subsets critical for autoimmune diseases.

Sho Yamasaki

Prof. Sho Yamasaki

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

STAFF

Asst. Prof. : Masamichi Nagae ／ Asst. Prof. : Eri Ishikawa ／ Postdoc. : Xiuyuan Lu ／ Postdoc. : Carla Guenther ／ Postdoc. : Shota Torigoe ／ Grad. Student 9

Publication

(1) *Helicobacter pylori* metabolites exacerbate gastritis through C-type lectin receptors. Nagata M., et al. ***J. Exp. Med.*** (2021) Jan 4;218(1):e20200815

(2) Structural insight into the recognition of pathogen-derived phosphoglycolipids by C-type lectin receptor DCAR. Omahdi Z., et al. ***J Biol Chem.*** (2020) 295(17):5807-5817

(3) Lipoteichoic acid anchor triggers Mincle to drive protective immunity against invasive group A Streptococcus infection.I mai T., et al. ***Proc. Natl. Acad. Sci USA.*** (2018) 115:E10662-71.

(4) Intracellular metabolite β-glucosylceramide is an endogenous Mincle ligand possessing immunostimulatory activity. Nagata M., et al. ***Proc. Natl. Acad. Sci. USA.*** (2017) 114:E3285-94

(5) Protein kinase D regulates positive selection of CD4(+) thymocytes through phosphorylation of SHP-1. Ishikawa E., et al. ***Nat. Commun.*** (2016) 7:12756.

(6) C-type lectin receptor DCAR recognizes mycobacterial phosphatidyl-inositol mannosides to promote a Th1 response during infection. Toyonaga K., et al. ***Immunity.*** (2016) 45:1245-57.

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

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

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

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

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

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

●Novel T cell subsets contribute to autoimmune diseases

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

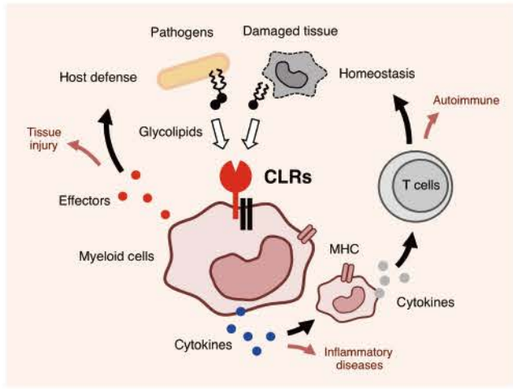


Fig1. Various Immune Responses triggered by CLRs

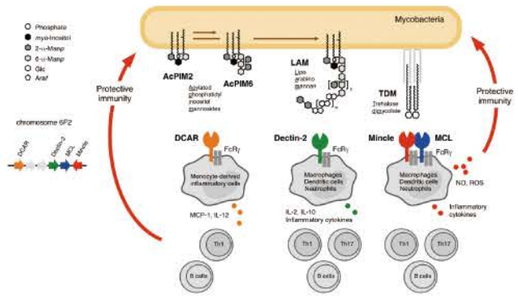


Fig. 2. Cooperative function of CLRs against mycobacteria

DEPT. OF HOST DEFENSE

Innate immunity is a defense system triggered by pattern recognition receptors, which recognize various pathogens including bacteria, fungi, and viruses, and induces the production of inflammatory factors to trigger the immune response. To gain the comprehensive understanding, our lab addresses novel genes associated with innate immunity and their molecular machinery.

Shizuo Akira (concur.)

SA Professor

Dr. Akira graduated from Osaka University Medical School in 1977 and received his Ph.D. from the same institution in 1984. He spent the period from 1985 to 1987 as a research fellow in the Department of Microbiology and Immunology at California University and then returned to the Institute for Molecular and Cellular Biology at Osaka University, where he remained until 1996. After working at Hyogo College of Medicine for three years, he served as a Professor at RIMD from 1999 to 2018. Having concurrently served as the Director for WPI Immunology Frontier Research Center (IFReC), Osaka University from 2007 to 2019, he was appointed as a SA professor at IFReC and concurrently at RIMD in 2018.

STAFF

SA Assoc. Prof. : Kazuhiko Maeda (concur.) ／
SA Lec. : Hiroki Tanaka (concur.) ／
SA Asst. Prof. : Kiyoharu Fukushima (concur.) ／
Undergrad. Student 1 ／ Grad. Student 7

Publication

(1) Dysregulated expression of the nuclear exosome targeting complex component Rbm7 in nonhematopoietic cells licences the development of Fibrosis. Fukushima et al. ***Immunity.***(2020) 52(3): 542-556.

(2) Phosphorylation-dependent Regnase-1 release from endoplasmic reticulum is critical in IL-17 response. Tanaka et al. ***J. Exp. Med.*** (2019) 216(6): 1431-1449.

(3) Regnase-1 controls colon epithelial regeneration via regulation of mTOR and purine metabolism. Nagahama et al. ***Proc Natl Acad Sci U S A.*** (2018) 115(43): 11036-11041.

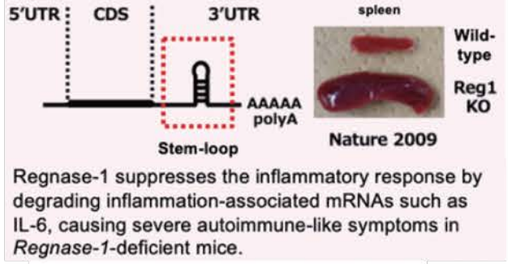
(4) Identification of an atypical monocyte and committed progenitor involved in fibrosis. Satoh et al. ***Nature.*** (2017) 541(7635): 96-101.

(5) Malt1-Induced Cleavage of Regnase-1 in CD4+ Helper T Cells Regulates Immune Activation. Uehata et al. ***Cell.*** (2013) 153(5):1036-1049.

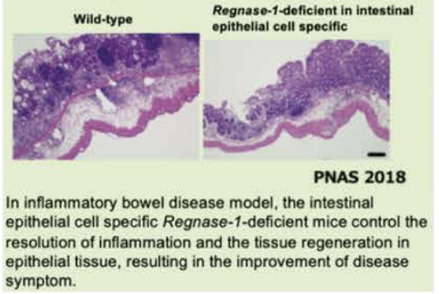
(6) Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Matsushita et al. ***Nature.*** (2009) 458 (7242):1185- 1190.

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

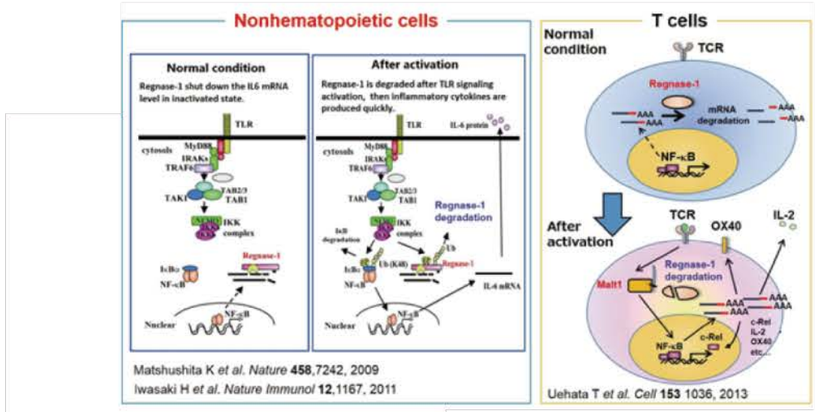
We have been investigating the comprehensive innate immune response induced by pattern recognition receptors that sense various pathogens. Based on the Toll-like receptor (TLR)-signaling, we propose a novel concept of "mRNA stability" in innate immunity, which orchestrates several immune events including inflammation and tissue homeostasis. Regnase-1, an endoribonuclease, constitutively degrades mRNAs encoding inflammatory cytokines. Once the TLR pathway is activated, the synthesis of mRNAs encoding inflammatory cytokines is induced, along with a reduction in Regnase-1 activity. 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. Temporary inactivation of Regnase-1 upon cellular activation is also found following stimulation with other proinflammatory cytokines or T-cell activation, suggesting the importance of Regnase-1 protein modification in the regulation of the innate immune response. Furthermore, we found that Regnase-1 not only regulates inflammation and immune activation, but also plays a critical role in tissue homeostasis through mRNA degradation. To understand the novel aspects of mRNA regulation by Regnase-1, we aim identify the Regnase-1 target genes associated with RNA metabolism in immune and non-immune cells.



Regnase-1 suppresses the inflammatory response by degrading inflammation-associated mRNAs such as IL-6, causing severe autoimmune-like symptoms in *Regnase-1*-deficient mice.



In inflammatory bowel disease model, the intestinal epithelial cell specific *Regnase-1*-deficient mice control the resolution of inflammation and the tissue regeneration in epithelial tissue, resulting in the improvement of disease symptom.



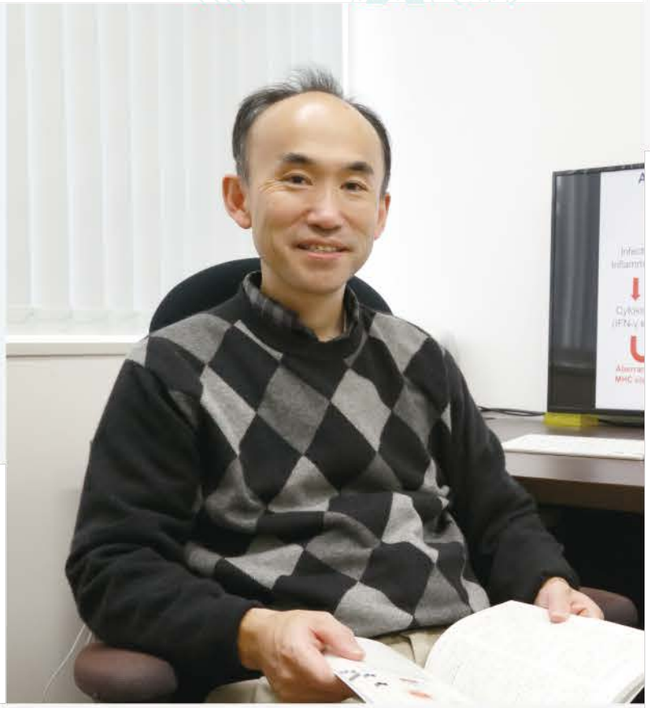
DEPT. OF IMMUNOCHEMISTRY

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.

Hisashi Arase (concur.)

Professor

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.



STAFF

Assoc. Prof. : Masako Kohyama ／ Asst. Prof. : Wataru Nakai ／ Postdoc. : Jin Hui ／ Grad. Student 4

Publication

(1) Immune evasion of Plasmodium falciparum by RIFIN via inhibitory receptors. Saito F et al. ***Nature*** (2017) 552:101–105. Saito F., et al.,

(2) 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.

(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.

●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).

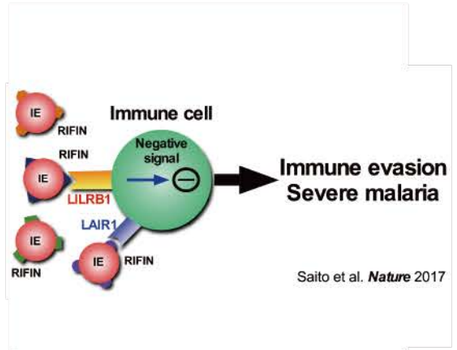


Fig. 1.
Inhibitory receptors play an important role in immune regulation, whereas pathogens exploit inhibitory receptors for immune evasion. We found malaria parasite has a mechanism to suppress the host immune response by using an inhibitory receptor, LILRB1, contributing to the pathogenesis of severe malaria.

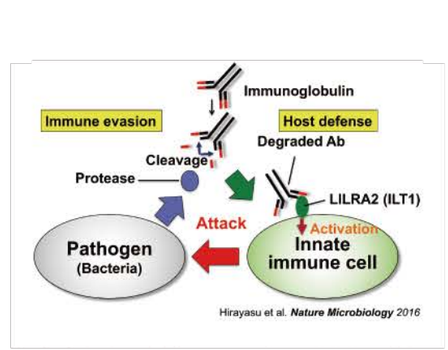


Fig. 2. Activating paired receptors play a role in host defense against bacterial infection
Activating paired receptor, LILRA2, recognizes immunoglobulin cleaved by bacterial protease activate innate immune cells (Hirayasu et al. Nat. Microbiol. 2016).

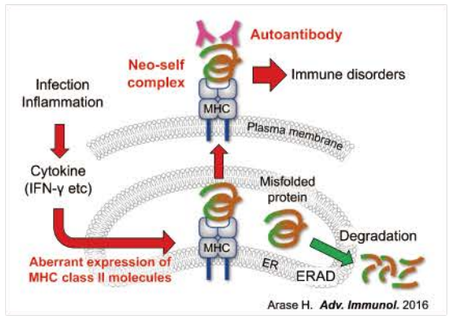


Fig. 3. Misfolded proteins complexed with MHC class II molecules are targets for autoantibodies.
Misfolded cellular proteins are transported to the cell surface without being processed to peptides by associating with MHC class II molecules in the ER. Furthermore, misfolded proteins complexed with MHC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

DEPT. OF IMMUNE RESPONSE DYNAMICS

We have been studying the interactions between the nervous and immune systems, with a special focus on how neural inputs control immune cell trafficking. Recently, we established a new project that aims to develop novel therapies for inflammatory diseases.

Kazuhiro Suzuki (concur.)

Professor

Dr. Kazuhiro Suzuki received his B.S. in Chemistry from the University of Tokyo in 1998 and M.D. from the Medical School of Osaka University in 2003. After completing a medical internship, he carried out his doctoral studies in the Graduate School of Medicine at Osaka University, and obtained his Ph.D. in Medicine in 2007. He trained as a postdoctoral fellow from 2007 to 2011 at the University of California, San Francisco. He returned to Osaka University as an associate professor and launched his independent laboratory at the Immunology Frontier Research Center (IFReC) in 2011. He was appointed as a professor at IFReC and concurrently at RIMD in 2017.

STAFF

Assist. Prof. : Akiko Nakai (concur.) ／
Posdoc : Sarah Leach ／ Grad. Student 4

Publication

(1) The COMMD3/8 complex determines GRK6 specificity for chemoattractant receptors. Nakai, A., et al. ***J. Exp. Med.*** (2019) 216: 1630-1647.

(2) Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes. Suzuki, K., et al. ***J. Exp. Med.*** (2016) 213: 2567-2574.

(3) Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors. Nakai, A., et al. ***J. Exp. Med.*** (2014) 211: 2583-2598.

(4) The sphingosine 1-phosphate receptor S1P2 maintains the homeostasis of germinal center B cells and promotes niche confinement. Green, J.A., et al. ***Nat. Immunol.*** (2011) 12: 672-680.

(5) Visualizing B cell capture of cognate antigen from follicular dendritic cells. Suzuki, K., et al. ***J. Exp. Med.*** (2009) 206: 1485-1493.

(6) Semaphorin 7A initiates T-cell-mediated inflammatory responses through α1β1 integrin. Suzuki, K., et al. ***Nature*** (2007) 446: 680-684.

●Immune regulation by the nervous system

Various aspects of the immune response have been shown to be influenced by the nervous system. Indeed, lymphoid organs are innervated by various types of neurons, and immune cells express neurotransmitter receptors in order to respond to neural inputs. However, little is known about how inputs from the nervous system control immune responses. To resolve this issue, we studied the cellular and molecular basis of the neural regulation of immunity. Adrenergic nerves constitute the efferent arc of the sympathetic nervous system. Like other vital organs, lymphoid organs, including the bone marrow, thymus, spleen, and lymph nodes, receive a rich supply of adrenergic nerves. We found that inputs from adrenergic nerves control lymphocyte egress from lymph nodes through β2-adrenergic receptors (Fig. 1). Additionally, our study demonstrated that this mechanism helps to generate a diurnal rhythm of the adaptive immune responses in the lymph nodes.

●Developing novel therapeutic strategies for inflammatory diseases

Lymphocyte migration is mediated by G protein-coupled receptors (GPCRs), which respond to different chemoattractants such as chemokines. In an effort to identify the novel factors involved in chemoattractant receptor signaling, we identified a protein complex consisting of copper metabolism MURR1 domain-containing (COMMD) 3 and COMMD8 (COMMD3/8 complex). The COMMD3/8 complex interacts with the C-terminal tail of chemoattractant receptors and promotes lymphocyte chemotaxis mediated by these receptors (Fig. 2). Deficiency in the COMMD3/8 complex severely impairs B cell migration and humoral immune responses in vivo. Therefore, the COMMD3/8 complex is essential for the proper functioning of the immune system. Our recent data suggest that the COMMD3/8 complex may be involved in the pathogenesis of inflammatory diseases. Pharmacological inhibition of the COMMD3/8 complex may provide a novel approach for the treatment of immune disorders.

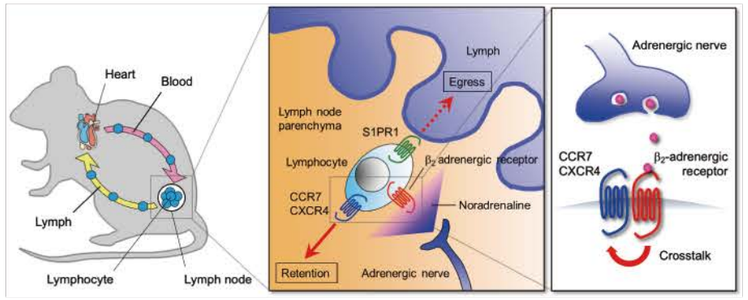


Fig. 1. Adrenergic control of lymphocyte egress from lymph nodes
Activation of β2-adrenergic receptors expressed on lymphocytes enhances the responsiveness of CCR7 and CXCR4, chemokine receptors that promote lymph node retention of lymphocytes, and inhibits their egress from lymph nodes.

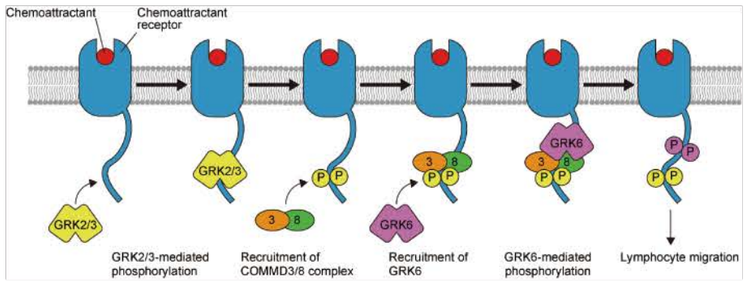


Fig. 2. Role of the COMMD3/8 complex in chemoattractant receptor signaling
The COMMD3/8 complex functions as an adaptor that recruits GPCR kinase (GRK) 6 to chemoattractant receptors, promoting MAPK activation and consequently lymphocyte chemotaxis.

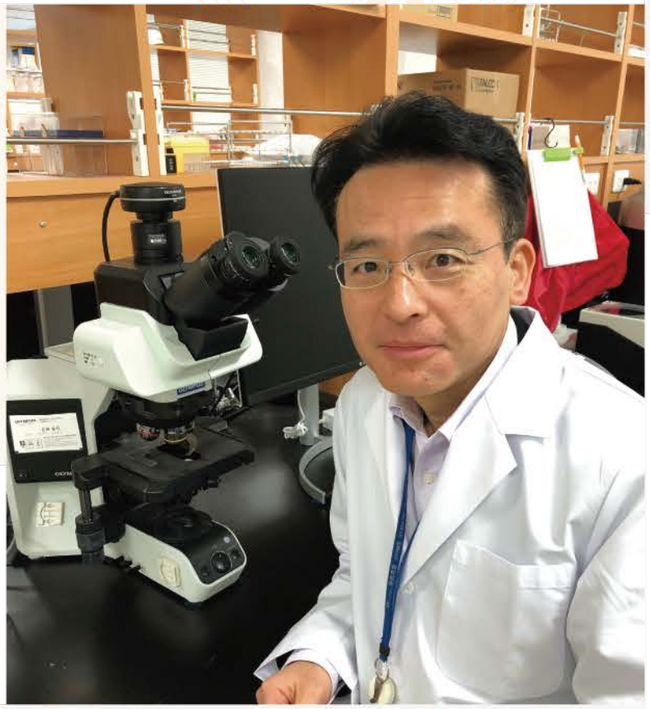
DEPT. OF MOLECULAR MICROBIOLOGY

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.

Eiji Hara (concur.)

Professor

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.



STAFF

Asst. Prof. : Shimpei Kawamoto ／ Asst. Prof. : Tomonori matsumoto ／ SA Asst. Prof. : Masahiro Wakita ／ Postdoc. : Tatsuyuki Matsudaira Postdoc. : Shunya Tsuji ／ Gard. Student 3

Publication

(1) A BET family protein degrader provokes senolysis by targeting NHEJ and autophagy in senescent cells. Wakita M. et al. ***Nat. Commun.*** (2020) 11:1935

(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/CCdh1 in senescent cells. Takahashi A., et al. ***Molecular Cell*** (2012) 45:123-31.

(4) Real-time in vivo imaging of p16Ink4a reveals cross-talk with p53. Yamakoshi K., et al. ***Journal of Cell Biology*** (2009) 186:393-407.

(5) Mitogenic signalling and the p16INK4a- 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 p16INK4a expression during cellular senescence. Ohtani N., et al. ***Nature*** (2001) 409:1067-70.

●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 p16INK4a and p21Waf1/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 p16INK4a or p21Waf1/Cip1 gene promoters. Using these senescence response reporter mice in combination with knockout mice, we are investigating the timing and, hence, the likely roles and mechanisms, of cellular senescence in vivo.

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

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

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

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

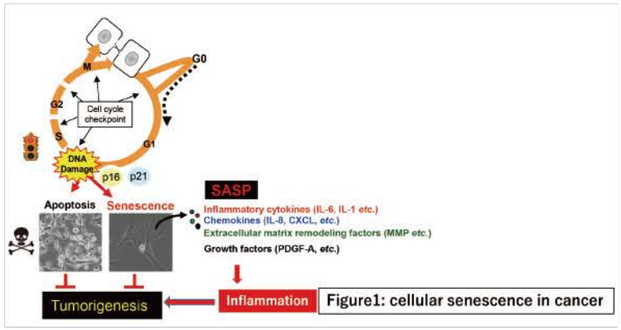


Fig. 1.
Cellular senescence initially inhibits proliferation of damaged cells, thereby acting as a fail-safe mechanism. However, in the long term, senescent cells may eventually promote tumorigenesis via SASPs.

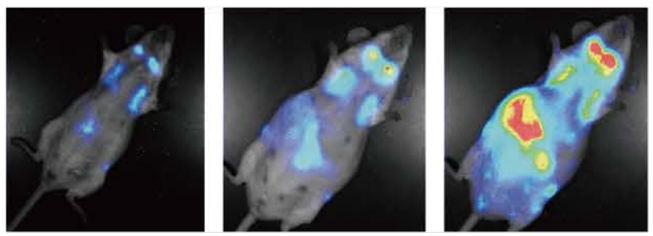
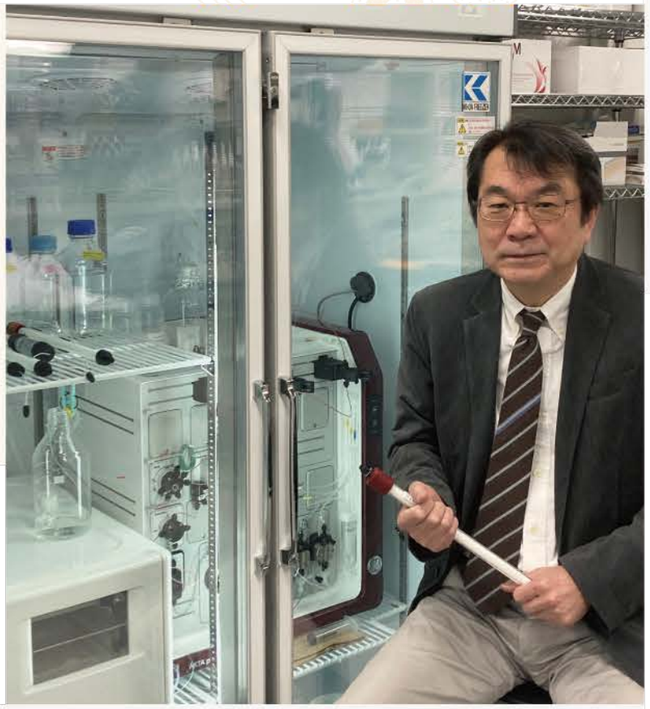


Fig. 2.Real-time bioluminescence imaging of p16INK4a gene expression during aging (Journal of Cell Biology 186: 393-407. 2009).

DEPT. 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.



Masato Okada

Professor

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.

STAFF

Assoc. Prof. : Shigeyuki Nada ／ Asst. Prof. : Kentaro Kajiwara ／ SA Asst. Prof. : Tetsuya Kimura ／ SA Asst. Prof. : Makoto Matsuda ／ SA Reseracher : Kanako Akamatsu ／ Grad. Student 10

Publication

(1) CDCP1 promotes compensatory renal growth by integrating Src and Met signaling. Kajiwara K. et. al. ***Life Science Alliance.*** 4 (4):e202000832, 2021.

(2) β-catenin-promoted cholesterol metabolism protects against cellular senescence in naked mole-rat cells. Chee W-Y. et. al. ***Communications Biol.*** 4(1):357, 2021.

(3) Amino Acids Enhance Polyubiquitination of Rheb and Its Binding to mTORC1 by Blocking Lysosomal ATXN3 Deubiquitinase Activity. Yao Y. et. al. ***Mol Cell.*** 80(3):437-451.e6, 2020.

(4) p18/Lamtor1-mTORC1 Signaling Controls Development of Mucin-producing Goblet Cells in the Intestine. Ito S. et. al. ***Cell Struct Funct.*** 45(2):93-105, 2020.

(5) Structural basis for the assembly of the Ragulator-Rag GTPase complex. Yonehara R., et al. ***Nature Commun.*** 8:1625, 2017.

(6) Polarization of M2 macrophages requires Lamtor1 that integrates cytokine and amino-acid signals. Kimura T., et al. ***Nat Commun.*** 7:13130, 2016.

●Src and cancer development

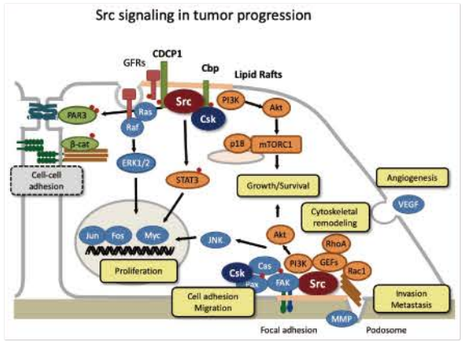
Src is a signaling molecule that localizes to the sub-membrane and was the first oncogene to be discovered. Normal tissues retain morphology by maintaining contact between neighboring cells via cell-cell junctions; however, cancer cells exhibit altered morphology (shown in Fig. 1) and undergo invasion 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.

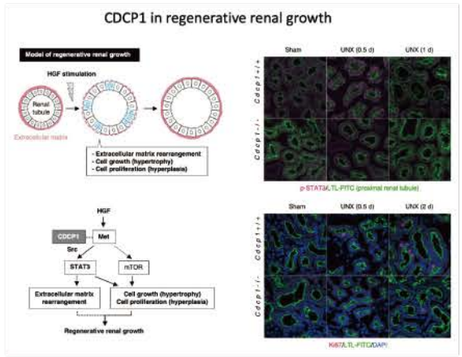
Interestingly, unlike other oncogenes, Src harbors no mutations. We found that Src is involved in a phenomenon called "cell competition," in which cells interact and compete with each other, producing a "winner" based on their relative fitness. We anticipate that revealing the relationship between Src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

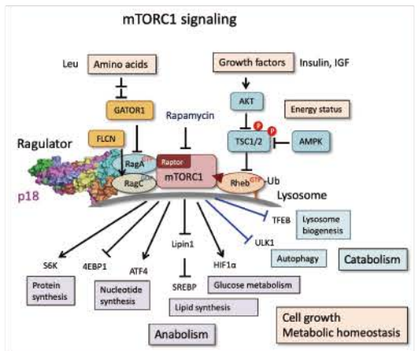
●The molecular mechanism underlying p18/Ragulator and mTOR nutrient signaling

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 (Fig.1). 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.







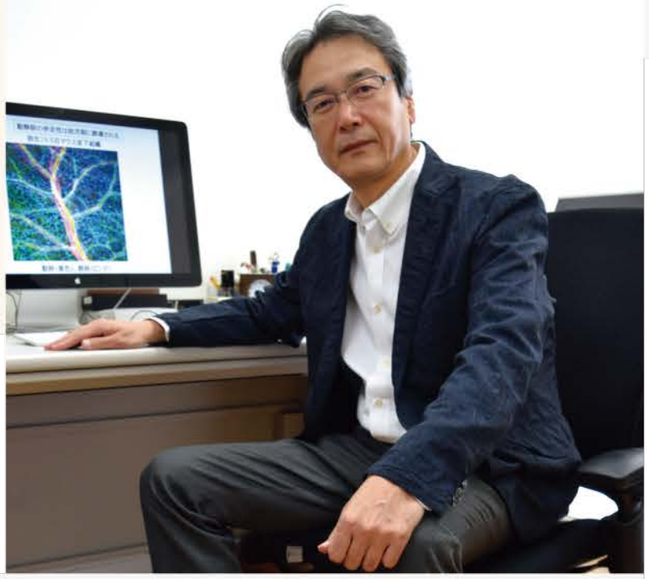
DEPT. OF SIGNAL TRANSDUCTION

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.

Nobuyuki Takakura

Professor

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.



STAFF

Assoc. Prof. Hiroyasu Kidoya ／ Postdoc. : Jia Wei Zhen ／ Postdoc. : Fumitaka Muramatsu ／ Postdoc. : Yumiko Hayashi ／ Postdoc. : Keigo Akuta ／ Postdoc. : Tomohiro Iba ／ Postdoc. : Zeynep Bal ／ Grad. Student 11

Publication

(1) Indispensable role of Galectin-3 in promoting quiescence of hematopoietic stem cells. Jia W. et al., ***Nature Commun.*** (2021) 12(1):2118.

(2) Regnase-1-mediated post-transcriptional regulation is essential for hematopoietic stem and progenitor cell homeostasis. Kidoya H. et al., ***Nat Commun.*** (2019) 10(1):1072.

(3) TAK1 prevents endothelial apoptosis and maintains vascular integrity. Naito h., et al., ***Dev Cell.*** (2019) 48(2):151-166.e7.

(4) CD157 marks tissue-resident endothelial stem cells with homeostatic and Regenerative properties. Wakabayashi T., et al. ***Cell Stem Cell*** 22(3):384-397, 2018.

(5) APJ regulates parallel juxtapositional alignment of arteries and veins in the skin. Kidoya H., et al. ***Dev Cell*** (2015) 33(3):247-59.

(6) A role for hematopoietic stem cells in promoting angiogenesis. Takakura N., et al. ***Cell*** (2000) 102(2):199-209.

●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).

●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.

●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.

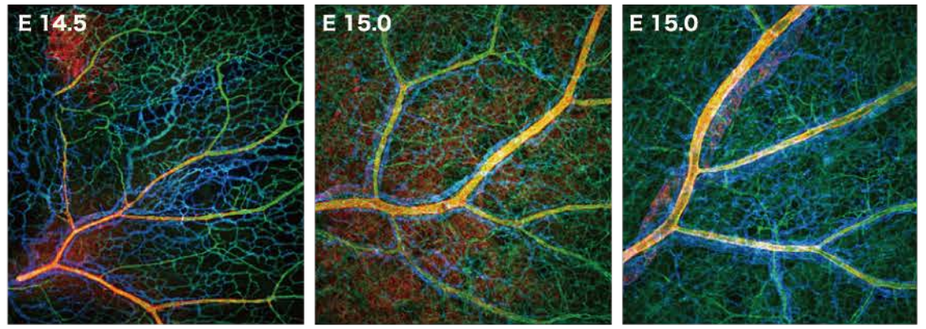


Fig. 1. Vascular development in mouse embryos. Hierarchal architecture of blood vessels accompanied by arterial (yellow)–venous (blue) alignment. Green; endothelial cells.

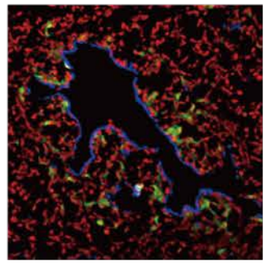


Fig. 2. Endothelial cells (blue) and CSCs (green) in a tumor. CSCs localize at the perivascular area, the so called "vascular niche."

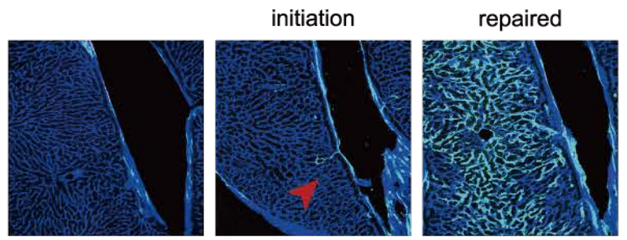


Fig3. Linage tracing of VESC. New blood vessels emerged from VESC (shown in green) Most of the endothelial cells (ECs) are replaced by ECs drived from VESC.

DEPT. 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.

Hiroaki Miki

Professor

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.

STAFF

Assoc. Prof. : Daisuke Yamazaki ／ Asst. Prof. : Yosuke Funato ／ Postdoc. : Osamu Hashizume ／ Grad. Student 8

Publication

(1) Structural basis for the Mg2+ recognition and regulation of the CorC Mg2+ transporter. Wu et al. ***Science Advances.*** (2021) Feb 10;7 (7):eabe6140.

(2) The oncogenic PRL protein causes acid addiction of cells by stimulating lysosomal exocytosis. Funato et al. ***Dev Cell.*** (2020) 55 (4):387-397.

(3) Excessive Mg2+ Impairs Intestinal Homeostasis by Enhanced Production of Adenosine Triphosphate and Reactive Oxygen Species. Hashizume et al. ***Antioxid Redox Signal.*** (2020) 33(1):20-34.

(4) Phosphocysteine in the PRL-CNNM pathway mediates magnesium homeostasis. Gulerez et al. ***EMBO Rep.*** (2016) 17(12):1890-1900.

(5) Membrane protein CNNM4-dependent Mg2+ efflux suppresses tumor progression. Funato et al. ***J Clin Invest.*** (2014) 124(12):5398-5410.

(6) Basolateral Mg2+ Extrusion via CNNM4 Mediates Transcellular Mg2+ Transport across Epithelia: A Mouse Model. Yamazaki et al. ***PLoS Genet.*** (2013) 9(12):e1003983.

●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 Mg2+ transporter, and inhibits its Mg2+ 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 Mg2+ 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.

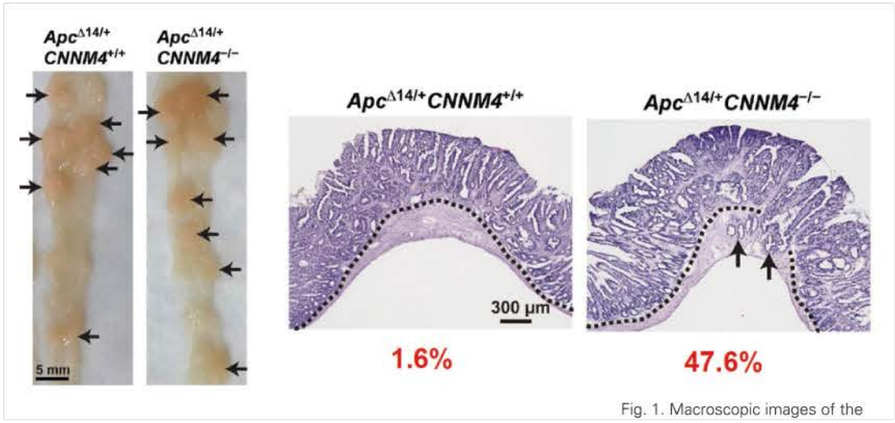


Fig. 1. Macroscopic images of the intestine (left) and histological images of polyps (right) in the indicated genetically engineered mice. CNNM4-deficient mice develop adenocarcinomas that invade the muscle layer (arrows).

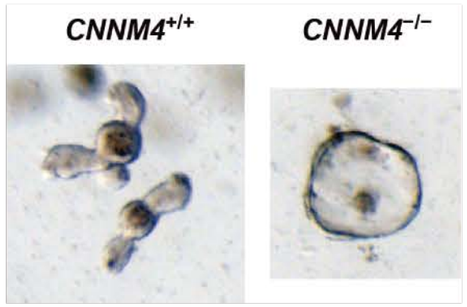
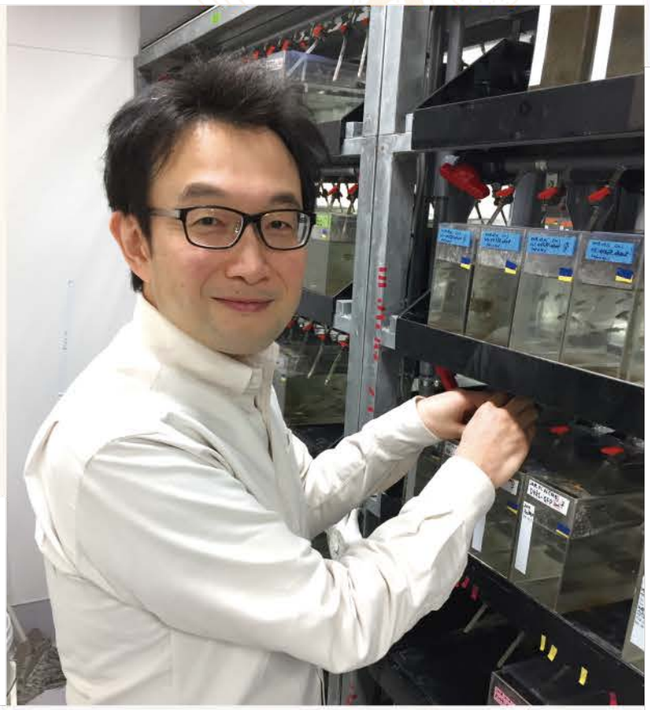


Fig. 2. Organoid culture of intestinal epithelia from the indicated genetically engineered mice. CNNM4 deficiency causes morphological abnormalities.

DEPT. OF HOMEOSTATIC REGULATION

In our body, cells recognize its position and roles via cell-cell communication and behave appropriately. Such cell behavior supports tissue morphogenesis and homeostasis, and its dysregulation is involved in congenital malformation, cancer, degenerative diseases, and aging. We focus especially on the cell-cell communication and behavior supporting tissue homeostasis and explore unknown molecular systems controlling embryonic development, organogenesis, regeneration, aging, and disease, using in vivo imaging, model animal genetics, molecular and cell biology, and biochemistry.



Tohru Ishitani

Professor

Prof. Ishitani received his Ph.D. from Nagoya University in 2002. After working as postdoctoral fellow in the same university, he became Associate Professor in the Medical Institute of Bioregulation, Kyushu University in 2006. He was appointed Professor in the Institute for Molecular and Cellular Regulation, Gunma University in 2017. He took his current position at RIMD in 2019. He received Young Scientists' Prize of The Commendation for Science and Technology by MEXT in 2009, and Samuro Kakiuchi Memorial Award by the Japanese Biochemical Society in 2014.

STAFF

Asst. Prof. : Masayuki Oginuma ／ Asst. Prof. : Yuki Akieda ／
SA Asst. Prof. : Shizuka Ishitani ／ JSPS Research Fellow PD : Kota Abe ／ JSPS Research Fellow PD : Kana Aoki ／
Undergrad. Student: 2 ／ Grad. Student 10

Publication

(1) Cell competition corrects noisy Wnt/β-catenin morphogen gradients to achieve robust patterning in the zebrafish embryo. Akieda Y., et al. ***Nat. Commun.*** (2019) 10: 4710

(2) Hipk2 and PP1c cooperate to maintain Dvl protein levels required for Wnt signal transduction. Shimizu N., et al. ***Cell Reports*** (2014) 8(5) 1391-1404

(3) Visualization and exploration of Tcf/Lef function using a highly responsive Wnt/β-catenin signaling-reporter transgenic zebrafish. Shimizu N., et ***Developmental biology*** (2012) 370(1) 71-85

(4) NLK positively regulates Wnt/β-catenin signalling by phosphorylating LEF1 in neural progenitor cells. Ota S., et al. ***EMBO Journal*** (2012) 31:1904-15

(5) Nemo-like kinase suppresses Notch signalling by interfering with formation of the Notch active transcriptional complex. Ishitani T., et al. ***Nat. Cell Biol.*** (2010) 12:278-85

(6) Nrarp functions to modulate neural-crest-cell differentiation by regulating LEF1 protein stability. Ishitani T., et al. ***Nat. Cell Biol.*** (2005) 7:1106-12

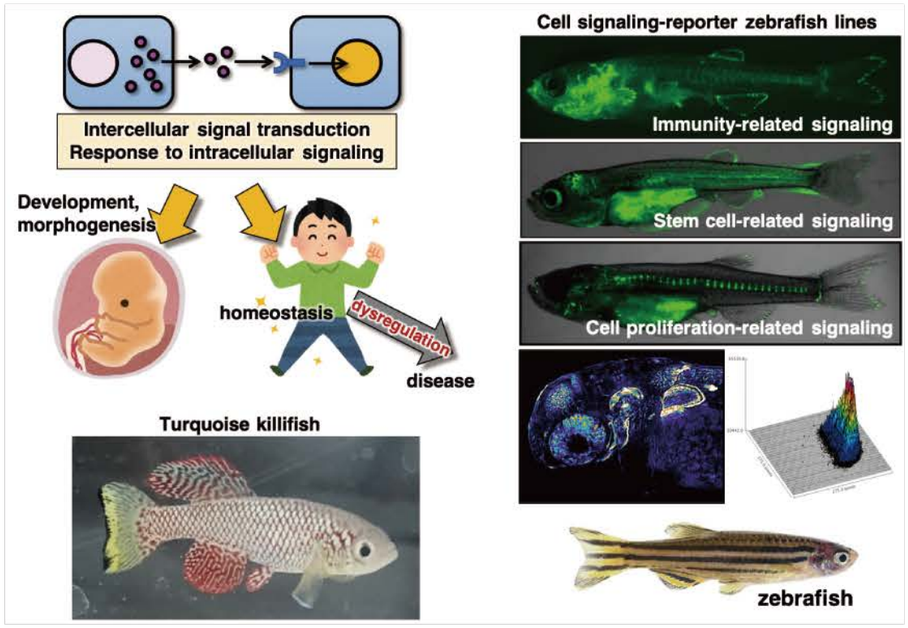
(7) The TAK1-NLK-MAPK-related pathway antagonizes signalling between beta-catenin and transcription factor TCF. Ishitani T., et al. ***Nature*** (1999) 399:798-802

●A new concept of tissue homeostasis "Morphostasis"

Developing animal tissues are reproducibly formed in the same shape even in the presence of internal fluctuations and external perturbations (developmental robustness). Adult tissues also maintain a stable morphology while replacing old or damaged cells with new healthy cells (tissue homeostasis), but its dysregulation is involved in various diseases. We are focusing common ground between "developmental robustness" and "tissue homeostasis" and regard it as "Morphostasis" . Specifically, using a zebrafish as a model animal which is suitable for in vivo imaging analysis of cell-cell communication and tissue dynamics and genetic analysis, we are exploring unknown molecular systems supporting developmental robustness and testing their potential roles in adult tissue homeostasis and their dysregulation in disease. We try to combine developmental biology and disease study to establish a new concept of tissue homeostasis.

●Aging program and its regulation

We are tackling the exploration of the molecular mechanisms underlying individual aging. Aging mechanisms have been studied using worm (C.elegans) and fly (Drosophila)as model animals because their life spans are very short. However, their organs are quite different from those of human. In addition, the life spans of mouse and zebrafish, which are well used as human disease model, are very long (3~4years). So, researchers have been searching for short-lived vertebrates. Our lab is using a short-lived fish "turquoise killifish" (the life span of which is 3~6months) as a new aging model. This fish shows age-dependent decline of motility, fertility, and cognitive function, similar to human. We are challenging the clarification of human aging mechanisms and the development of new technique extending "healthy life expectancy" , using turquoise killifish!



DEPT. 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.

Masahito Ikawa

Professor

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 two 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, SSR Research Award in 2017 and Japanese Association for Laboratory Animal Science 2021・Ando-Tajima Award. His lifework is to study mammalian reproductive systems using genetically engineered mice.

STAFF

Assoc. Prof. : Haruhiko Miyata / Assoc. : Norikazu Yabuta (concur.) / Asst. Prof. : Keisuke Shimada (concur.) / Asst. Prof. : Daiji Kiyozumi / Asst. Prof. : Chihiro Emori (concur.) / SA Asst. Prof. : Tsutomu Endo (concur.) / SA Asst. Prof. : Julio Castaneda / SA Asst. Prof. : Yonggang Lu / Research Fellow : Rie Iida / JSPS Research Fellow : Seiya Oura / JSPS Research Fellow : Kiyonori Kobayashi / Guest Prof. : Martin M. Matzuk / Guest Assoc. Prof. : Yoshitaka Fujihara / Guest Assoc. Prof. : Taichi Noda / Guest Researcher : Masaru Okabe / Undergrad. Student 5 / Grad. Student 3

Publication

(1) ARMC12 regulates spatiotemporal mitochondrial dynamics during spermiogenesis and is required for male fertility. Shimada K., ***PNAS.*** 2021 Feb 9;118(6):e2018355118.

(2) Bi-allelic DNAH8 Variants Lead to Multiple Morphological Abnormalities of the Sperm Flagella and Primary Male Infertility. Liu C., et al. ***Am J Hum Genet.*** 2020 Aug 6;107 (2):330-341.

(3) NELL2-mediated lumicrine signaling through OVCH2 is required for male fertility. Kiyozumi D., et al. ***Science.*** 2020 Jun 5;368 (6495):1132-1135.

(4) Sperm proteins SOF1, TMEM95, and SPACA6 are required for sperm-oocyte fusion in mice. Noda T., et al. ***PNAS.*** 2020 May 26;117 (21):11493-11502.

(5) Spermatozoa lacking Fertilization Influencing Membrane Protein (FIMP) fail to fuse with oocytes in mice. Fujihara Y., et al. ***PNAS.*** 2020 Apr 28;117(17):9393-9400.

(6) Sperm calcineurin inhibition prevents mouse fertility with implications for male contraceptive. Miyata H., ***Science.*** 2015 Oct 23;350(6259):442-5.

●Analysis of molecular mechanisms involved in mammalian reproduction

Our laboratory focuses to mechanistically study the mammalian reproduction system in vivo using gene-manipulated animals. We were the first laboratory in the world to produce genetically modified mice that express a green fluorescent protein (GFP) throughout the body (Fig. 1). These green fluorescent mice are useful for many types of research projects. Indeed, we used these animals to label sperm with a fluorescent protein and visualized the fertilization process (Exp Anim. 2010; JCS. 2010, 2012; PNAS. 2012, 2013) (Fig. 2).

We introduced the cutting edge CRISPR/Cas9 system and have been improving the technology (SciRep. 2013, 2016; Science 2018). By utilizing the system, we have recently elucidated the lumicrine system; testis derived NELL2 go through the male reproductive tract's luminal space and triggers differentiation of epididymal epithelial cells through ROS1 receptor kinase. Then, activated epididymal cells secrets OVCH2 protease that modulate sperm fertilizing ability by trimming sperm membrane ADAM3 protein (Publication 3). We also found that sperm calcineurin (PPP3CC/PPP3R2) is essential for sperm motility and male fertility (publication 6). Inhibiting sperm calcineurin may lead to the development of a reversible male contraceptive.

More recently, besides IZUMO1 (Nature 2005), we found novel sperm proteins essential for the sperm-oocyte fusion process (Publications 4 and 5). Our laboratory will continue elucidating the mammalian fertilization mechanism.

●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.

Our laboratory and the Animal Resource Center for Infectious Diseases support services such as the generation of genetically modified animals, in vitro fertilization, and cryopreservation of mouse strains.

For more information about our research and services, please visit our homepage (https://egr.biken.osaka-u.ac.jp/).

Fig. 1. GFP-expressing mice. Our "Green mice" have been used for more than hundreds of researchers and are good models for studying human disease (FEBS Lett 1997;407:313-319).

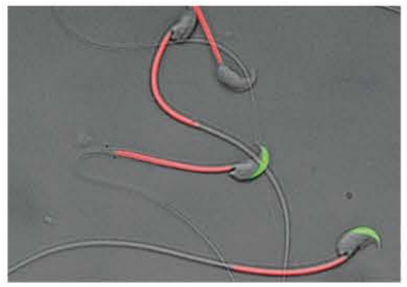


Fig. 2. RBGS sperm. Transgenic spermatozoa carrying GFP and dDsRed2 in their acrosome and mitochondria. These gametes are useful to visualize the fertilization process (Exp Anim 2010;59:105-107).

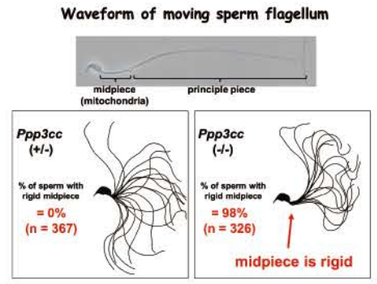


Fig. 3. Calcineurin deficient sperm. Serm calcineurin is required for sperm motility for successful fertilization (Science 2015;350:442-445).

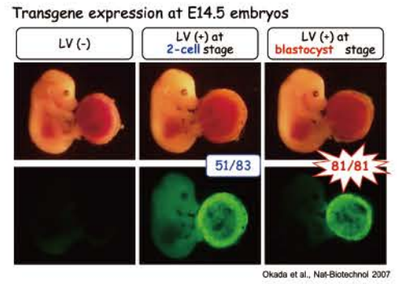


Fig. 4. Lentirival vector-mediated transgenesis in mice. Lentiviral vectors are not able to transduce eggs with zona pellucida (ZP) (left). Without ZP, transductions of fertilized egg and blastocyst result in the whole transgenic (middle) and placenta-specific transgenic (right), respectively (Nat Biotechnol 2007;25:233-237).

DEPT. OF GENOME INFORMATICS

We use single cell sequencing along with computational methods to study problems that are difficult or impossible to observe by experimental methods alone. Some of the problems we work on include: analysis of B and T cell receptor repertoires, protein-nucleotide interactions and multiple sequence alignment of protein and nucleotide sequences. These themes are described in more detail below.

Daron M. Standley

Professor

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

STAFF

Assoc. Prof. : Kazutaka Katoh ／ Assoc. Prof. : Shunsuke Teraguchi (concur.) ／ Asst. Prof. : Songling Li ／ Postdoc. : Floris J.Van Eerden ／ Postdoc. : John Rozewicki ／ Postdoc. : Jan Wilamowski ／ Visiting Researcher : Mara Llamas-Covarrubias Anais ／ Grad. Student 6

Publication

(1) MAFFT multiple sequence alignment software version 7: improvements in performance and usability. Katoh, K., et al. ***Mol Biol Evol*** (2013) 30(4) 772-80

(2) MAFFT-DASH: integrated protein sequence and structural alignment. Rozewicki J., et al. ***Nucleic Acids Research*** (2019) 47(1)5-10

(3) Repertoire Builder: High-throughput structural modeling of B and T cell receptors. Schritt D., et al. ***Mol. Syst. Des. Eng.*** (2019) 4, 761-768

(4) Functional clustering of B cell receptors using sequence and structural features. Xu Z., et al. ***Mol. Syst. Des. Eng.*** (2019) 4, 769-778

(5) Structural Modeling of Lymphocyte Receptors and Their Antigens. Li S., et al. ***Methods Mol Biol.*** (2019) 2048:207-229.

(6) Regnase-1 and Roquin Regulate a Common Element in Inflammatory mRNAs by Spatiotemporally Distinct Mechanisms. Mino, T., et al. ***Cell*** (2015)161, 1058-1073

●Multiple sequence alignment

Multiple sequence alignment (MSA) is an important step in many computational biology pipelines and MAFFT is one of the most popular programs for building MSAs1[1]. Since the first release of MAFFT in 2002, we have been continuously improving its accuracy, speed and utility in practical situations, and have provided different options for newly emerging types of data and analyses. Recent features include: inclusion of secondary structural information of non-coding RNAs and proteins, interactive selection of sequences for phylogenetic tree inference, and integration of protein sequences with comprehensive structural alignments[2]. The latter feature plays a central role in structural modeling methods in our lab.

●Analysis of B and T cell receptor specificity and repertoires

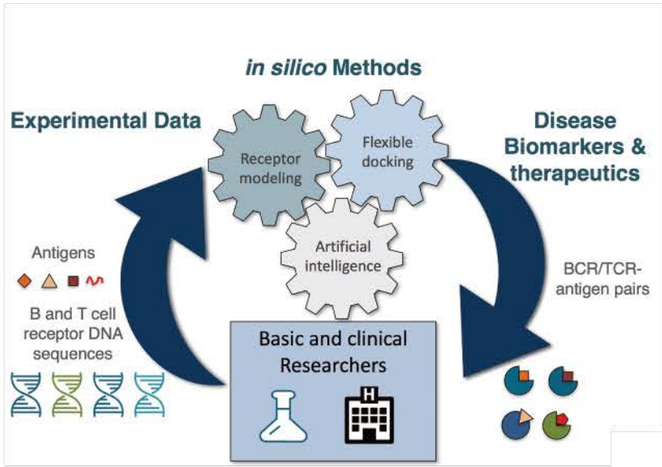
Prediction of B and T cell receptor antigen specificities from sequence is currently an important and open problem. Our lab is approaching this challenge using a combination of B and T cell receptor sequencing, structural modeling and artificial intelligence. We have developed a tool for generating BCR and TCR 3D models in a high-throughput and accurate manner[3]. We have further extended this technology to cluster such models according to their antigen and epitope specificity[4]. We have also developed a tool to build TCR-epitope-MHC structural models from sequence[5] and are working on new BCR epitope prediction methods that make use of structural information. The immediate goals of this research are to identify antigens and epitopes that are associated with specific diseases along with the B or T cell receptors that recognize these antigens and epitopes.

●Sequencing B and T cell receptors

A healthy immune system maintains a vast repertoire of B and T cells that can recognize a wide range of molecules. B and T cell receptors are produced by the combination of two highly variable polypeptide chains which are encoded by different mRNA transcripts. Due to the high variability of each polypeptide and the combination of two different molecules, each individual' s repertoire of receptors is in general unique. Several immunological and molecular methodologies have been employed to study the immune repertoire with a rather low-resolution. Nevertheless, the advent of next generation sequencing (NGS) has allowed to analyze millions of immune receptor sequences in one sample (bulk sequencing). This has been of great value to the study of immune repertoires, but cannot reveal the pairing of receptor sequences. In the past few years, single cell sequencing technologies have emerged and have made it possible to study paired polypeptide chains from thousands of individual B and T cells. We are currently making use of both bulk and single cell sequencing techniques to study immune cell repertoires in health and disease.

●Protein-nucleotide interactions

Protein-nucleotide interactions play a central role in the flow of biological information in all living systems. In the immune system, the importance of DNA-binding proteins in the regulation of transcription has been studied extensively. More recently, the importance of RNA-binding proteins (RBPs) in maintenance of homeostasis as well as in shaping the strength and duration of immune responses post-transcriptionally has been noted[6]. In order to gain further insight into the mechanisms of RBP-mediated immune regulation, we are developing tools for nucleotide binding site prediction and flexible protein-nucleotide docking which have been validated in a number of experimental studies.



DEPT. OF INFECTION METAGENOMICS

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

Tetsuya Iida (concur.)

Professor

STAFF

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

Publication

(1) Pulmonary disease caused by a newly identified mycobacterium: Mycolicibacterium toneyamachuris: a case report. Kuge T., et al. ***BMC Infect Dis.*** 2020 Nov 25;20(1):888.

(2) Comprehensive subspecies identification of 175 nontuberculous mycobacteria species based on 7547 genomic profiles. Matsumoto Y., et al. ***Emerg Microbes Infect.*** 2019;8 (1):1043-1053.

(3) Deep learning approach for pathogen detection through shotgun metagenomics sequence classification. Hsu YF, et al. Proceedings - ***AIME 2019*** 17th Conference on Artificial Intelligence in Medicine. 2019, 2011526, 26-29.

(4) Interplay of a secreted protein with type IVb pilus for efficient enterotoxigenic Escherichia coli colonization. Oki H., et al. ***Proc Natl Acad Sci U S A.*** 2018 Jul 10;115 (28):7422-7427.

(5) Fungal ITS1 Deep-Sequencing Strategies to Reconstruct the Composition of a 26-Species Community and Evaluation of the Gut Mycobiota of Healthy Japanese Individuals. Motooka D., et al. ***Front Microbiol.*** 2017 Feb 15;8:238.

●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.

●Study of gut flora during onset of infectious disease

It is becoming clear that the gut microbiota 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. 1.Large scale computer system for NGS data analysis.

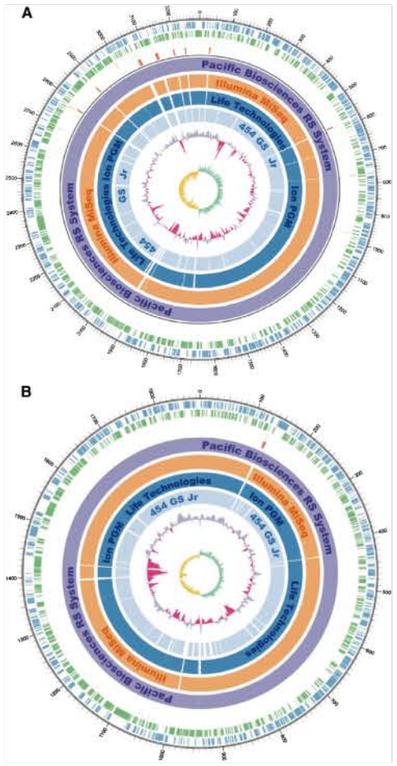


Fig. 2.
Genomic analysis of Vibrio parahaemolyticus using four models of next-generation sequencer: 454 GS Jr(Roche)、IonPGM(Life Technologies)、MiSeq(Illumina)、Pacific Biosciences RS System (PacBio)
GS Jr, MiSeq, and IonPGM produce short reads. Therefore, they require assembly of short fragments. The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

NEXT-GENERATION SEQUENCING(NGS) CORE FACILITY

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

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

Next Generation Sequencers: NovaSeq 6000 (Illumina) and DNBSEQ-G400 (MGI)

Single cell isolatiors:Chromium™ Controller (10X Genomics) and Rhapsody™ Express (BD)

STAFF

Head, Prof. : Sho Yamasaki (concur.) ／
SA Assoc. Prof. : Shota Nakamura (concur.) ／
SA Assoc. Prof. : Daisuke Okuzaki ／
Asst. Prof. : Daisuke Motooka

Publication

(1) Serine racemase enhances growth of colorectal cancer by producing pyruvate from serine. Ohshima K., ea al. ***Nat Metab.*** 2020 Jan;2(1):81-96.

(2) Identification of a novel arthritis-associated osteoclast precursor macrophage regulated by FoxM. Hasegawa T., ea al. ***Nat Immunol.*** 2019 Dec;20 (12):1631-1643.

(3) UNAGI: an automated pipeline for nanopore full-length cDNA sequencing uncovers novel transcripts and isoforms in yeast. Al Kadi M., et al. ***Funct Integr Genomics.*** 2020 Jul;20(4):523-536.

(4) Regnase-1 controls colon epithelial regeneration via regulation of mTOR and purine metabolism. Nagahama Y., et al. ***Proc Natl Acad Sci U S A.*** 2018 Oct 23;115(43):11036-11041.

THE RIMD HISTORY MUSEUM

The RIMD History Museum was launched as a 70th anniversary memorial project of the Research Institute for Microbial Diseases (RIMD) and opened in 2010. Many historical items related to RIMD are on display. This museum is open to the public and more than 10,000 people have been visite this museum.

Opening Ceremony at December 17th, 2010

At the Ceremony, Dr. Hitoshi Kikutani (the then RIMD Director, middle in the photo), Dr. Higashi Yasushi (the then Director General of BIKEN foundation, right in the photo) and Mr. Tokuharu Takeo (descendant of Jiemon Takeo, who is contributed to Takeo Research Institute, a research institute merged to RIMD in 1934, left in the photo)

RIMD Chronology and Koch' s Microscope

Samples shown by Microscope

Research History at RIMD

Location : RIMD Main Building 1F
Open : 9:00~17:00 Weekdays
Free of charge
http://www.biken.osaka-u.ac.jp/museum/

DEPT. 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.

Tetsuya Iida

Professor

Dr. Iida graduated Faculty of Science, Kyoto University in 1984 and 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.

STAFF

Assoc. Prof. : Shigeaki Matsuda ／
SA Asst. Prof. : Pranee Somboonthum ／
Grad. Student 5

Publication

(1) Export of a Vibrio parahaemolyticus toxin by the Sec and type III secretion machineries in tandem. Matsuda S., et al. ***Nat. Microbiol.*** (2019) 4:781-8

(2) 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.

(3) 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.

(4) 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.

(5) 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.

(6) Metagenomic diagnosis of bacterial infections. Nakamura S., et al. ***Emerg Infect Dis.*** (2008) 14(11):1784-6.

●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.

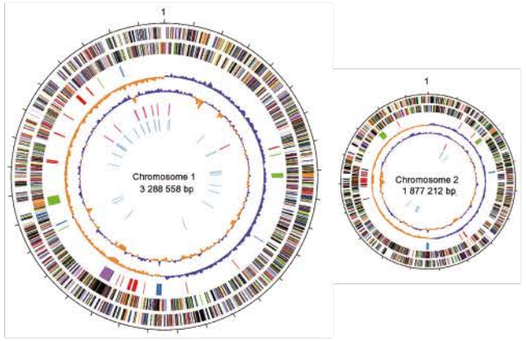


Fig. 1. The genomes of bacteria belonging to genus Vibrio comprise two distinct circular chromosomes. (Lancet, 2003)

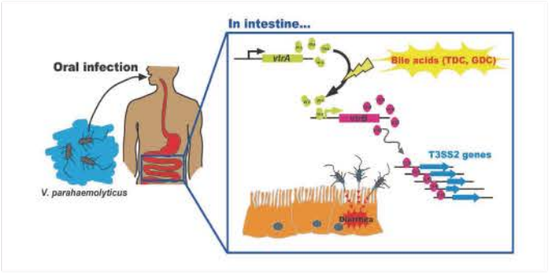


Fig. 2. Bile in the small intestine induces expression of genes encoding T3SS2, which is the major virulence factor produced by Vibrio parahaemolyticus, the causative agent of diarrhea.

DEPT. OF MOLECULAR PROTOZOOLOGY

Malaria is a mosquito-borne infectious disease and is caused by infection with Plasmodium species. Its burden exceeds 200 million infections every year, resulting in more than 400,000 deaths annually. Plasmodium parasites have the complex life cycle between host animals and mosquitos. They specifically express the genes at each developmental stage during the life cycle and those stage-specific genes are essential for invasion, parasitizing, and multiplication. Our research interest is how the parasite regulate the gene expression stage-specifically. To elucidate it, we focus on the sequence-specific transcriptional factor and characterize them by the genetic engineering technique and the next generation sequencing. The expected result will be useful for understanding the molecular basis of the parasite's life cycle, but also for exploring the drug target and vaccine antigens.

Shiroh Iwanaga

Professor

Received B.Sc. (1994) and Ph.D. (1999) form Kyushu University. Promoted to assistant professor at Dept. of Agriculture of Kobe University (1999), lecturer at Dept. of Medicine of Tottori University (2007), associate professor at the graduate school of medicine of Mie University (2009), and professor at the graduate school of medical and dental science of Tokyo Medical and Dental Universtiy. Appointed current position as a professor of RIMD in 2020.

STAFF

Asst.Prof. : Toshiyuki Mori ／
SA Asst.Prof. : Mai Nakashima ／
Postdoc. : Akihito Sakoguchi

Publication

(1) Improvement of CRISPR/Cas9 system by transfecting Cas9-expressing Plasmodium berghei withlinear donor template. Shinzawa N. et. al. ***Commun Biol.*** (2020) 3(1):426.

(2) Female-specific gene regulation in malaria parasites by an AP2-family transcription factor. Yuda M. et. Al. ***Mol Microbiol.*** (2019)113(1) 40-51.

(3) Global transcriptional repression: An initial and essential step for Plasmodium sexual development. Yuda M. et.al. ***Proc. Natl. Acad. Sci. U S A.*** (2015)112(41),12824-9.

(4) Genome-Wide Identification of the Target Genes of AP2-O, a Plasmodium AP2-Family Transcription Factor. Kaneko I. et.al., ***PLoS Pathog.*** (2015)11(5):e1004905.

(5) A high-coverage artificial chromosome library for the genome-wide screening of drug-resistance genes in malaria parasites. Iwanaga S.et.al., ***Genome Res.***(2012) 22 (5):985-92.

(6) Functional Identification of the Plasmodium Centromere and Generation of a Plasmodium Artificial Chromosome. Iwanaga S. et.al., ***Cell, Host & Microbe.***(2010) 7(3):245

●Transcriptional regulation of Plasmodium parasites.

Plasmodium parasites have the complex life cycle between host animals and mosquito vector (see: https://www.cdc.gov-/malaria/about/biology/index.html). In the course of the life cycle, the parasite change their morphology dramatically and infect specifically various cells of host animal and vectors. The stage-specific gene expression allow the morphological change and acquirement of infectivity to cells and is thus essential for the completion of this complex life cycle. The transcriptional regulation plays an important role in this stage-specific gene expression. However, the transcriptional factors had not been identified even after completion of whole genome sequencing, the mechanism of transcriptional regulation was not elucidated. We firstly demonstrated that the Apetala2 (AP2) protein family is the sequence-specific transcriptional factor of Plasmodium parasites. AP2 transcription factors express stage-specifically, and further directly and comprehensively controls the transcription of all genes involved in stage formation at each developmental stage. Our group now attempt to identify target genes of all AP2 transcription factors using next generation sequencing technology, such as chromatin-immunoprecipitation sequencing. Based on the obtained information, we attempt to elucidate mechanism of transcriptional regulation for entire life cycle.

●From Plasmodium artificial chromosome to Synthetic Plasmodium parasites.

In the previous study, we generated Plasmodium artificial chromosome (9.0 kbp), which consists of centromere, telomere and replication origin. It segregates into daughter parasites with more than 99.9 % efficiency during nuclear division and is maintained as single copy by the function of centromere. In addition, its telomere functions properly, which protects the ends. We further combined artificial chromosomes of Plasmodium parasite and budding yeasts and generated a shuttle artificial chromosome, which can behave like actual chromosomes in both living organism. We now attempt to synthesize parasite's genome in budding yeast and to transplant the resultant synthetic genome into Plasmodium parasite. The transgenic parasites, in which synthetic genome will be transplanted, will be first synthetic eukaryotic cells and will be utilized for synthetic biological research. Furthermore, it will be utilized for designing artificial attenuated parasites, which will be safety live vaccine for malaria.

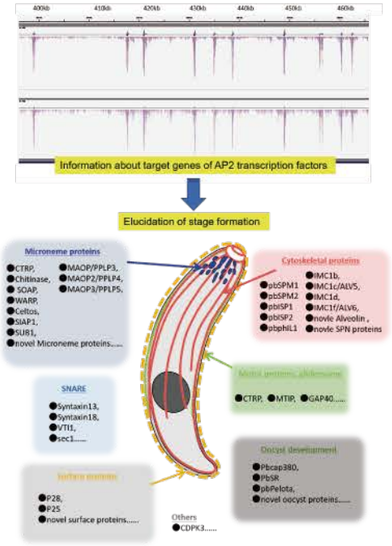


Fig. 1: Chromatin-immunoprecipitation sequencing analysis shows that AP2 transcription factor binds to the promoter region of target genes specifically. The information of target genes is useful for our understanding the formation of developmental stage. This figure shows the summary of the target genes in ookinete, which is the mosquito midgut invasion stage.

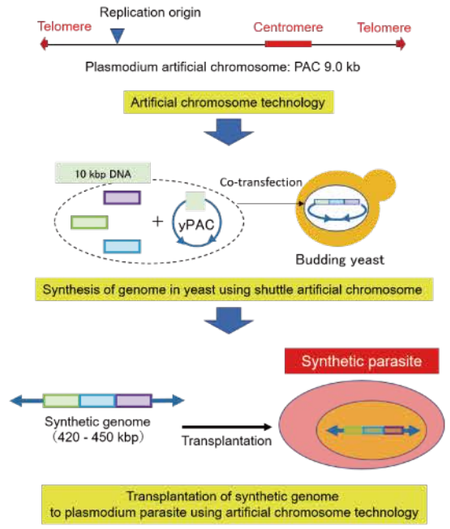


Fig. 2: Plasmodium artificial chromosome consists of centromere, telomere, and replication origin. The shuttle artificial chromosome, yPAC, is generated by combining Plasmodium and Yeast artificial chromosomes. The genome of Plasmodium parasites can be synthesized using YAC in budding yeast. The synthetic Plasmodium parasites can be generated by transplanting synthetic genome into parasites.

DEPT. OF VIROLOGY

The family Reoviridae comprises a group of nonenveloped viruses classified into 15 genera, and possessing 9–12 segmented double-stranded RNA genomes. This family includes important pathogens, including the rotaviruses, in humans and animals. In our laboratory, using original technology to generate recombinant *Reoviridae* viruses from cloned cDNAs, we are studying molecular mechanisms underlying *Reoviridae* virus replication and pathogenesis, and developing novel vaccine vectors.

Takeshi Kobayashi

Professor

Dr. Kobayashi received his Ph.D. from Osaka University in 2000. He became a Research associate at RIMD in the same year. He spent for five years as a postdoctoral fellow in Vanderbilt University, USA before returning to Japan to work at the Institute for Virus Research in Kyoto University. He was appointed SA Associate Professor of RIMD in 2012. He is in his current position from 2020.

STAFF

Assoc. Prof. : Yuta Kanai ／ Asst.Prof. : Tomohiro Kotaki ／ Postdoc. : Shohei Minami ／ Grad. Student 3

Publication

(1) Reverse Genetics Approach for Developing Rotavirus Vaccine Candidates Carrying VP4 and VP7 Genes Cloned from Clinical Isolates of Human Rotavirus. Kanai Y., et al. ***J Virol.*** 2020 Dec 22;95(2):e01374-20.

(2) Generation of Genetically RGD σ1-Modified Oncolytic Reovirus That Enhances JAM-A-Independent Infection of Tumor Cells. Kawagishi T., et al. ***J Virol.*** 2020 Nov 9;94 (23):e01703-20.

(3) Reverse Genetics System for a Human Group A Rotavirus. Kawagishi T., et al. ***J Virol.*** 2020 Jan 6;94(2):e00963-19

(4) In Vivo Live Imaging of Oncolytic Mammalian Orthoreovirus Expressing NanoLuc Luciferase in Tumor Xenograft Mice. Kanai Y., et al. ***J Virol.*** 2019 Jun 28;93(14):e00401-19.

(5) Cell-cell fusion induced by reovirus FAST proteins enhances replication and pathogenicity of non-enveloped dsRNA viruses. Kanai Y., et al. ***PLoS Pathog.*** 2019 Apr 25;15(4):e1007675.

(6) Entirely plasmid-based reverse genetics system for rotaviruses. Kanai Y., et al. ***Proc Natl Acad Sci U S A.*** 2017 Feb 28;114 (9):2349-2354.

●Rotavirus

Rotaviruses (RVs) are important pathogens that cause severe diarrhea in infants and young children worldwide. Current RV vaccines reduce the number of RV-associated deaths, but RV is still responsible for an estimated 228,047 annual deaths worldwide. RV, members of the family *Reoviridae*, have 11-segmented double-stranded RNA genomes contained within non-enveloped, triple-layered virus particles. Understanding of the molecular mechanisms underlying replication and pathogenesis has been hampered by lack of a reverse genetics system that allows synthesis of recombinant viruses from artificial genes. Recently, we developed a long-awaited plasmid-based reverse genetics system for RVs that opens up new avenues for studying RV replication and pathogenesis. Using this technology, we developed a stable RV reporter expression system and a vaccine platform by generating recombinant RVs carrying outer capsid VP4 or VP7 genes cloned from human RV clinical samples within the simian RV genetic backbone. We continue to investigate RV biology, and develop vaccines and therapeutics using a combination of genetic, biochemical, and biophysical approaches.

●Mammalian orthoreovirus

Mammalian orthoreoviruses (reoviruses) are members of the family *Reoviridae* possessing a genome composed of 10 segments of double-stranded RNA. Reoviruses are highly tractable experimental models for studying replication and pathogenesis of double-stranded RNA viruses. In the last decade, reoviruses have been evaluated in animal models and humans as oncolytic agents against a variety of tumors, (including head and neck, colon, breast, and pancreatic) due to the observation that reoviruses induce apoptosis/tumor cell death via an activated Ras signaling pathway. Wild-type reovirus-based oncolytic therapies are safe, but their efficacy is currently limited. We recently developed a reovirus reporter expression system using reovirus reverse genetics and used it for non-invasive imaging of reovirus infection in tumor xenograft mice. We also developed a reverse genetics system using a highly oncolytic reovirus strain. Using these systems, we are developing safer, more effective reovirus-based cancer therapeutics by genetic modification.

●Nelson Bay orthoreovirus

Nelson Bay orthoreovirus (NBV) was isolated from a flying fox in 1968. Until recently, it has not been associated with disease. However, NBVs were recently isolated from human patients suffering from acute respiratory tract infections in Malaysia, Indonesia, China, and Japan. These isolates have raised increasing concerns about bat-transmitted reovirus infections in humans. We established a reverse genetics system to understand molecular mechanisms underlying NBV replication. Using this system, we found that the cell attachment protein sigmaC, and the fusion-associated small transmembrane proteins are not necessary for viral replication, but play critical roles in viral pathogenesis. We are investigating *in vitro* and *in vivo* how NBV replicates and causes disease. Our aim is to develop vaccines, diagnostics, and therapeutics for pathogenic bat-borne reoviruses.

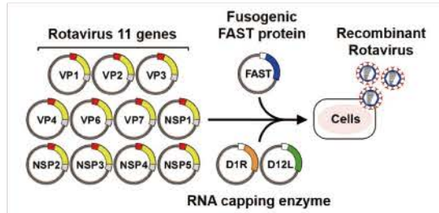


Fig. 1. Generation of recombinant rotaviruses from cloned cDNAs. BHK-T7 cell lines were transfected with the rotavirus 11 cDNA constructs and expression plasmids encoding FAST and vaccinia virus capping enzyme (D1R and D12L).

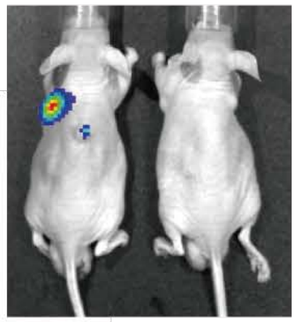


Fig. 2. Bioluminescence imaging of reovirus infection in human cancer xenografts. BALB/c nude mice transplanted with a human cancer cell line were infected intravenously with reporter reovirus.

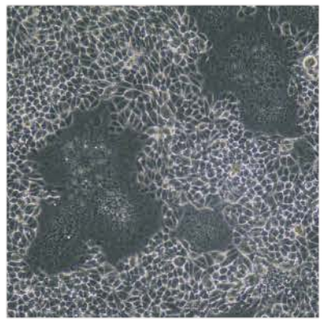


Fig. 3. Nelson Bay orthoreovirus is capable of inducing cell–cell fusion in infected cells.

LABORATORY OF VIRUS CONTROL

Our research is designed to elucidate the virus-host interactions involved in viral infection and pathogenicity. We develop therapeutic drugs and preventative programs for various viral infections based on our research results, with the aim of controlling infectious viruses in the human population.

Yoshiharu Matsuura

SA Professor

Dr. Matsuura received his PhD from Hokkaido University 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 served as Director of RIMD from 2015-2019. He was appointed as a director of Center for Infectious Disease Education and Research (CiDER).

STAFF

SA Assoc. Prof. : Shuhei Taguwa ／
SA Assoc. Prof. : Saya Nakagomi ／
Guest Assoc. Prof. : Chikako Ono ／
Postdoc. : Shiho Torii ／ Grad. Student 3

Publication

(1) Establishment of a reverse genetics system for SARS-CoV-2 using circular polymerase extension reaction. Torii S., et al., ***Cell Reports*** (2021) 35(3):109014.

(2) Various miRNAs compensate the role of miR-122 on HCV replication. Ono C., et al., ***PLoS Pathog.*** (2020) 16(6):e1008308.

(3) Host ESCRT factors are recruited during chikungunya virus infection and are required for the intracellular viral replication cycle. Torii S., et al., ***J Biol Chem.*** (2020) 295 (23):7941-7957.

(4) In vivo dynamics of reporter Flaviviridae viruses. Tamura T., et al., ***J Virol.*** (2019) 93 (22):e01191-19.

(5) USP15 participates in HCV propagation through the regulation of viral RNA translation and lipid droplet formation. Kusakabe S., et al., ***J Virol.*** (2019) 93(6):e01708-18.

(6) Infection with flaviviruses requires BCLXL for cell survival. Suzuki T., et al., ***PLoS Pathog.*** (2018) 14(9):e1007299.

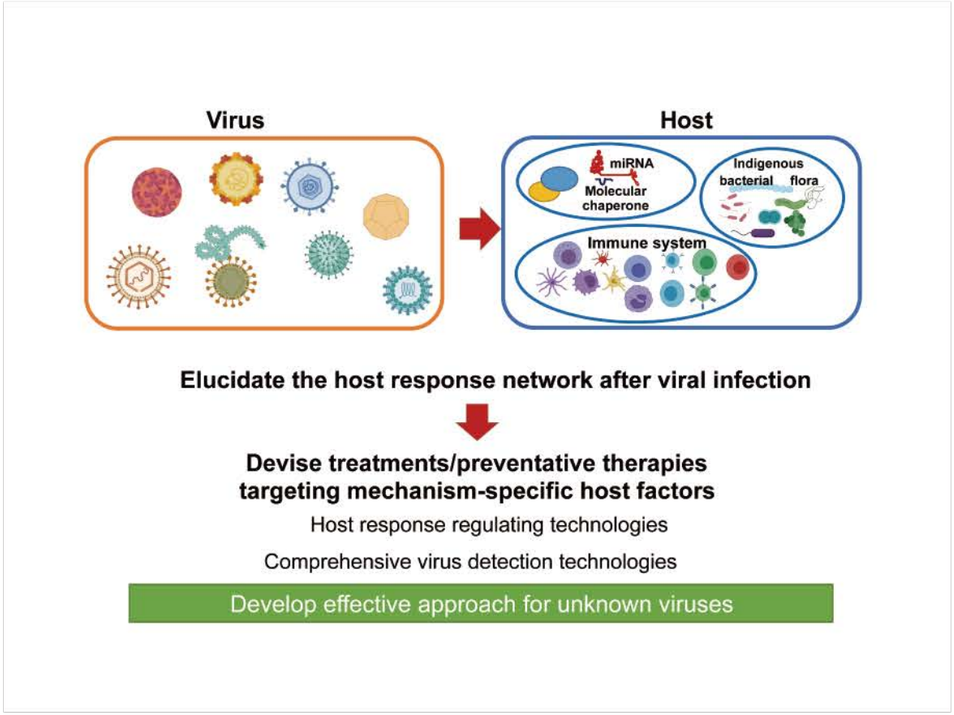
●Analyzing the host-virus interaction network

With the changing climate and rapid expansion of human activity, modern society is plagued by countless emerging viral infections, which significantly damage both societies and economies. However, as revealed by the novel coronavirus (SARS-Cov-2) pandemic, it is difficult to predict outbreaks of emerging viral infections, and the development of control measures can be too late. We conduct research designed to develop a comprehensive understanding of the pathogenic mechanisms underlying viral infections using host-virus interactions in an attempt to enable the pre-emptive development of viral prophylactics and treatment strategies.

Specifically, we intend to create an animal model capable of reproducing human like viral pathogenesis in order to better characterize host responses to viral infection. This research is done in collaboration with researchers in immunology and molecular imaging allowing us to obtain more comprehensive data. This data will aid collaborations with researchers in data science and facilitate the construction of mathematical models of host response patterns. These data will enable the classification of viral infections by host response patterns, and facilitate of the development of new treatments targeting the host factors involved in the biological responses specific to each pattern.

●Developing tools for viral research

To elucidate the pathogenesis of viruses and develop novel treatments and prevention strategies, researchers require tools that can quantify viral infectivity. We have developed a novel system for RNA virus research which includes the production of infective cDNA clones, virus-like particles, and pseudotype viruses to enable the study of highly virulent diseases without specialized BSL3 or 4 facilities. This system will be provided to the larger research community in the hope of accelerating viral research.



LABORATORY OF EMERGING VIRAL DISEASES

Mammarenaviruses include highly pathogenic agents such as Lassa (West Africa) and Junin (South America) viruses, which cause viral hemorrhagic fever in humans and pose important public health problems within their regions of endemicity. In addition, the worldwide-distributed, prototypic mammarenavirus, lymphocytic choriomeningitis virus (LCMV) is a neglected human pathogen of clinical significance. Despite their substantial impact on human health, current therapeutic options for mammarenaviruses are very limited. Our research focuses on investigating the molecular and cellular biology of mammarenaviruses to facilitate the development of novel antivirals and vaccines.

Masaharu Iwasaki

SA Associate Professor

Dr. Masaharu Iwasaki received his Ph.D. from Kyushu University for his work on measles virus RNA synthesis and virion assembly in 2010 and graduated from Kyushu University School of Medicine (MD-PhD program) in 2012. Thereafter, he worked as a Research Associate (2012), a Senior Research Associate (2015), and a Staff Scientist (2017) at The Scripps Research Institute, where he studied the molecular mechanisms underlying mammarenavirus multiplication. He was appointed to his current position in 2018.

Publication

(1) A Lassa Virus Live-Attenuated Vaccine Candidate Based on Rearrangement of the Intergenic Region.Cai Y. et al., ***mBio*** (2020) 11(2):e00186-20.

(2) Interactome analysis of the lymphocytic choriomeningitis virus nucleoprotein in infected cells reveals ATPase Na+/K+ transporting subunit Alpha 1 and prohibitin as host-cell factors involved in the life cycle of mammarenaviruses. Iwasaki M. et al., ***PLoS Pathog.*** (2018) 14(2):e1006892

(3) General Molecular Strategy for Development of Arenavirus Live-Attenuated Vaccines. Iwasaki M. et al., ***J Virol.*** (2015) 89 (23):12166-77.

(4) Sodium Hydrogen Exchangers Contribute to Arenavirus Cell Entry. Iwasaki M. et al., ***J Virol.*** (2014) 88 (1):643-54.

STAFF

Postdoc. : Mei Hashizume ／ Grad. Student 2

Mammarenaviruses are simple enveloped viruses with a bi-segmented ambisense RNA genome encoding four genes (Figure A). Each RNA segment, small (S) and large (L), directs the synthesis of two viral proteins from two open reading frames, which are separated by a non-coding intergenic region (IGR). Despite this simple genome organization, we know very little about the mechanisms by which these viruses multiply and cause disease in infected hosts. To better understand the complex biology of mammarenaviruses and to develop antiviral strategies that can combat these viruses, we use reverse genetics systems to generate recombinant mammarenaviruses, which contain pre-determined mutations and/or additional foreign genes such as enhanced green fluorescent protein (eGFP), from cloned cDNAs. We used these technologies to generate a recombinant LCMV harboring a synthetic LCMV S-IGR-like IGR instead of the L-IGR [rLCMV(IGR/S-Ssyn)] (Figure B). rLCMV(IGR/S-Ssyn) was severely attenuated in vivo but elicited protective immunity against a lethal challenge with wild-type LCMV. This strategy can be used to generate live-attenuated vaccines for currently known and potentially newly emerging hemorrhagic fever-causing mammarenaviruses without the need to incorporate amino acid changes. In addition, we generated recombinant LCMVs expressing eGFP or an affinity-tagged viral protein to facilitate genetic and pharmacological screenings and proteomic analyses with the aim of identifying virus-host interactions required for efficient multiplication of mammarenaviruses that can be exploited as druggable targets.

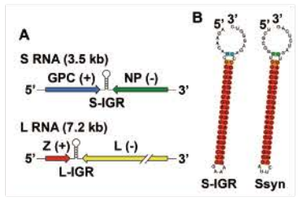


Fig. (A) Schematic diagram of the genome organization of mammarenaviruses. (B) Predicted RNA secondary structures of the LCMV S-IGR (left) and the synthetic LCMV S-IGR-like IGR (right).

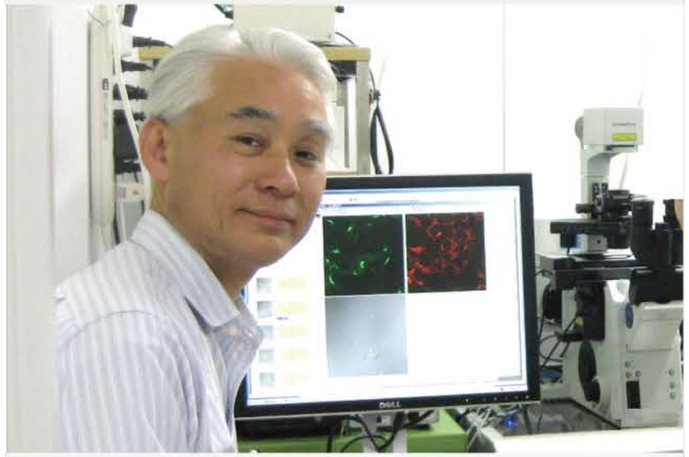
LABORATORY OF VIRAL DYNAMISM RESEARCH

The virus dynamism research group studies a variety of RNA viruses including the chikungunya virus (CHIKV) and severe fever with thrombocytopenia syndrome virus (SFTSV) which they use as model systems to expand our understanding of these infectious diseases and aid in the development of novel control mechanisms. This group focuses on understanding the interactions between the virus and the host and work to identify critical host factors involved in entry, proliferation, and viral release.

Yusuke Maeda

SA Professor

Dr. Maeda received his M.D. from Osaka University in 1988 and his Ph.D. from Osaka University in 1995. He was appointed as a research associate at RIMD in 1997 and in 1999 spent two and a half years working as a postdoctoral fellow at the UCSD in the USA . He was later appointed as an associate professor at RIMD in 2002 and has been in his current position since 2020.



Publication

(1) Anti-chikungunya virus monoclonal antibody inhibiting viral fusion and release. Tumkosit U. et al., ***J. Virol.*** In press

(2) The use of green fluorescent protein-tagged virus-like particles as a tracer in the early phase of chikungunya infection. Tumkosit U. et al., ***Virus Res.*** (2019) 272:197732.

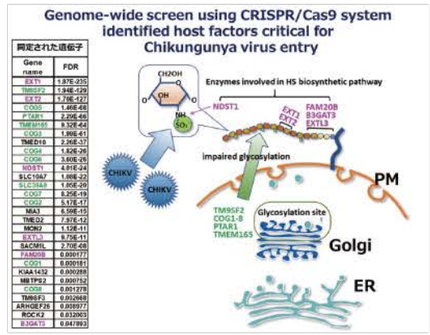
(3) Genome-wide screening uncovers the significance of N-sulfation of heparan sulfate as a host cell factor for Chikungunya virus infection. Tanaka A. et al., ***J. Virol.*** (2017) JVI.00432-17.

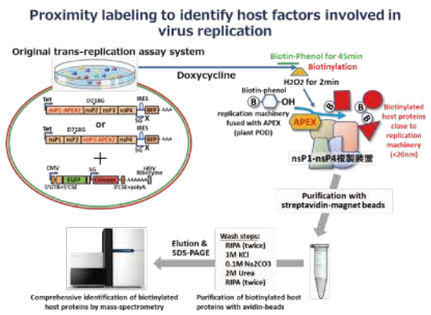
(4) Post-Golgi anterograde transport requires GARP-dependent endosome-to-TGN retrograde transport. Hirata T. et al., ***Mol. Biol. Cell*** (2015) 26(17):3071-84.

(5) GPI-glycan remodeling by PGAP5 regulates transport of GPI-anchored proteins from the ER to the Golgi. Fujita M. et.al, ***Cell*** (2009) 139(2): 352-365

(6) GPHR is a novel anion channel critical for acidification and functions of the Golgi apparatus. Maeda Y. et al., ***Nat. Cell Biol.*** (2008) 10(10): 1135-45.

This fundamental research is supported by our original assay systems, including the trans-replication and reporter cell lines developed in house. These tools are combined with molecular biology techniques, such as genome-wide screening (reverse genetics) and gene knockout/knockdown (forward genetics), cell biology techniques, such as microscopic analysis of organelles and vesicle transport, and biochemical techniques, such as protein-protein interactions and post-protein translational modifications (such as sugar chain and ADP-ribosylation) to unravel the complex multifactorial systems underlying viral infection. We have also implemented several projects focused in the novel coronavirus, which is an urgent social issue and thus an important consideration for our RIMD society.





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, Prof. : Tetsuya Iida (concur.)

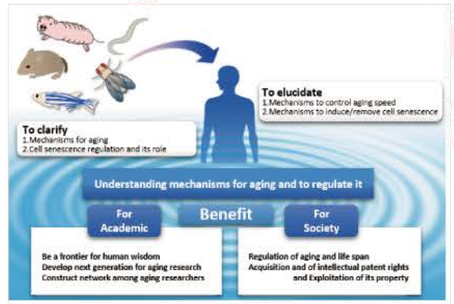
Collection list:
http://rceid.biken.osaka-u.ac.jp

RESEARCH CENTER FOR MECHANISM AND REGULATION OF AGING

The life expectancy of humans has increased markedly over recent decades. Ironically, this has resulted in a startling rise in the incidence of aging-associated diseases, resulting in serious social problems such as increased medical expenses and nursing care costs. To solve these problems, the Research Center for Mechanism and Regulation of Aging was established in 2017. The center aims to clarify the fundamental mechanisms that regulate aging and to understand the role of cellular senescence in aging and aging-associated diseases.

STAFF

Director, Prof. : Eiji Hara (concur.)



■ Division of Aging Model Organism

Dept. of Aging Rate Biology	Head: Invited Professor Eisuke Nishida RIKEN Center for Biosystems Dynamics Research
Dept. of Research of Signals Regulating Aging	Head: Invited Professor Naoki Hisamoto Group of Signaling Mechanisms, Graduate School of Science, Nagoya University
Dept. of Genetics and Metabolism	Head: Invited Professor Masayuki Miura Dept. of Genetics, Graduate School of Pharmaceutical Sciences, University of Tokyo
Dept. of Cell-cell Communication	Head: Invited Professor Tatsushi Igaki Lab. of Genetics, Graduate School of Biostudies, Kyoto University
Dept. of Organismal Aging Research	Head: Cocurrent Professor Tohru Ishitani Dept. of Homeostatic regulation, Research Institute for Mcrobial Diseases, Osaka University
Dept. of Autophagy and Aging	Head: Concurrent Professor Tamotsu Yoshimori Lab. of Intracellular Membrane Dynamics, Graduate School of Frontier Biosciences, Osaka University
Dept. of Sleep and Aging Regulation	Head: Invited Researcher Akiko Sato National Center for Geriatrics and Gerontology
Dept. of Reproductive Aging	Head: Concurrent Professor Masahito Ikawa Dept. of Experimental Research, Research Institute for Microbial Diseases, Osaka University
Dept. of Animal Longevity and Aging Research	Head: Invited Associate Professor Kyoko Miura Laboratory for Molecular Biology of Aging and Longevity, Faculty of Life Sciences, Kumamoto University

■ Division of Cellular Senescence

Dept. of Cell Senescence Mechanism	Head: Concurrent Professor Eiji Hara Dept. of Molecular Microbiology, Research Institute for Microbial Diseases, Osaka University
Dept. of Aging-associated Stress Signaling	Head: Invited Professor Hidenori Ichijo Lab. of Cell Signaling, Graduate School of Pharmaceutical Sciences, The University of Tokyo
Dept. of Senescent Cell Morphology & Motility	Head: Invited Professor: Yasuhiro Minami Dept. of Physiology and Cell Biology, Graduate School of Medicine, Kobe University
Dept. of Senescence Regulation	Head: Invited Professor Nakanishi Makoto Div. of Cancer Cell Biology, The Insitute of Medical Science, The University of Tokyo
Dept. of Transposon-Mediated Processes	Head: Invited Professor Haruhiko Shiomi Dept. of Molecular Biology, Keio University School of Medicine
Dept. of Senescent Metabolism	Head: Invited Researcher Tomonori Kimura KAGAMI Project, National Institutes of Biomedical Innovation, Health and Nutrition
Dept. of Immune Aging	Head: Invited Professor Yoko Hamazaki Dept. of Life Science Frontiers, Center for iPS Cell Research and Application, Kyoto University
Dept. of Brain Aging	Head: Invited Researcher Kiyohito Mizutani Div. of Pathogenic Signaling, Graduate School of Medicine, Kobe University

YABUMOTO DEPT. OF INTRACTABLE DISEASE RESEARCH

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

STAFF

Postdoc. : Wang Yicheng ／
Grad. Student 2

Taroh Kinoshita

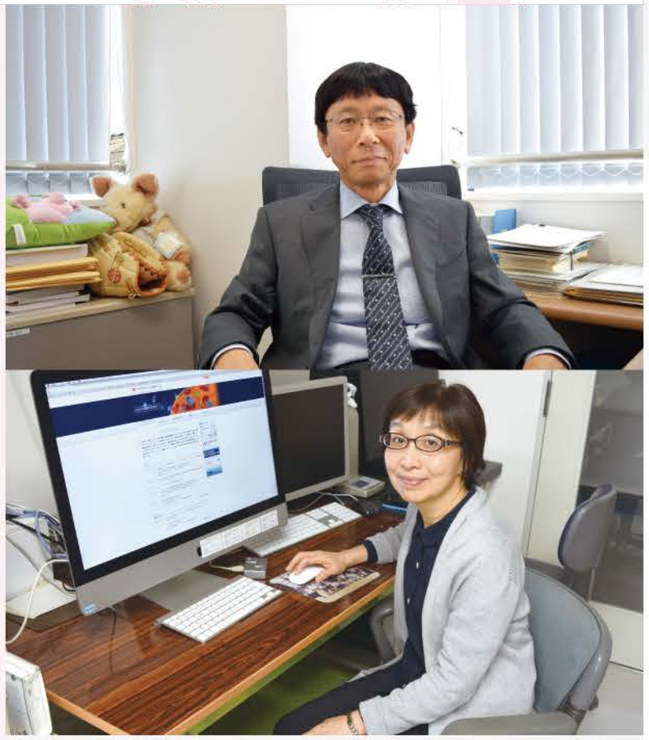
Endowed Chair Professor

Dr. Kinoshita received Ph.D. from Osaka University in 1981. After working at Department of Bacteriology, Osaka University Medical School and Department of Pathology, New York University School of Medicine, he appointed as a Professor in RIMD in 1990. He served as a Director of RIMD from 2003 to 2007. He concurrently serves as a Professor in Osaka University Immunology Frontier Research Center from 2007. From 2017, he is in the current position. 2017 Takeda Medical Prize, 2018 Medal with Purple ribbon.

Yoshiko Murakami

SA Professor

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



Publication

(1) Paroxysmal nocturnal hemoglobinuria caused by CN-LOH of constitutional PIGB mutation and 70-kbp microdeletion on 15q Langemeijer S. et al. ***Blood Adv.*** (2020) 4(22):5755-5761.

(2) Cross-talks of glycosylphosphatidylinositol biosynthesis with glycosphingolipid biosynthesis and ER-associated degradation.Wang Y et al. ***Nat. Commun.*** 2020 Feb 13;11(1):860.

(3) Complement and inflammasome overactivation mediates paroxysmal nocturnal hemoglobinuria with auto inflammation. Höchsmann B.et al.***J Clin Invest.*** (2019) 129 (12):5123-5136.

(4) Mutations in PIGB cause an inherited GPI biosynthesis defect with an axonal neuropathy and metabolic abnormality in the severe cases Murakami Y. et al. (2019) ***Am. J. Hum. Genet.***, 105:384-394.

(5) Identification of a Golgi GPI-N-acetylgalactosamine transferase with tandem transmembrane regions in the catalytic domain. Hirata, T., et al. ***Nat. Commun.*** (2018) 9:405.

(6) Phenotype-genotype correlations of PIGO deficiency with variable phenotypes from infantile lethality to mild learning difficulties. Tanigawa, J., et al. ***Hum. Mutat.*** (2017) 38:805-815.

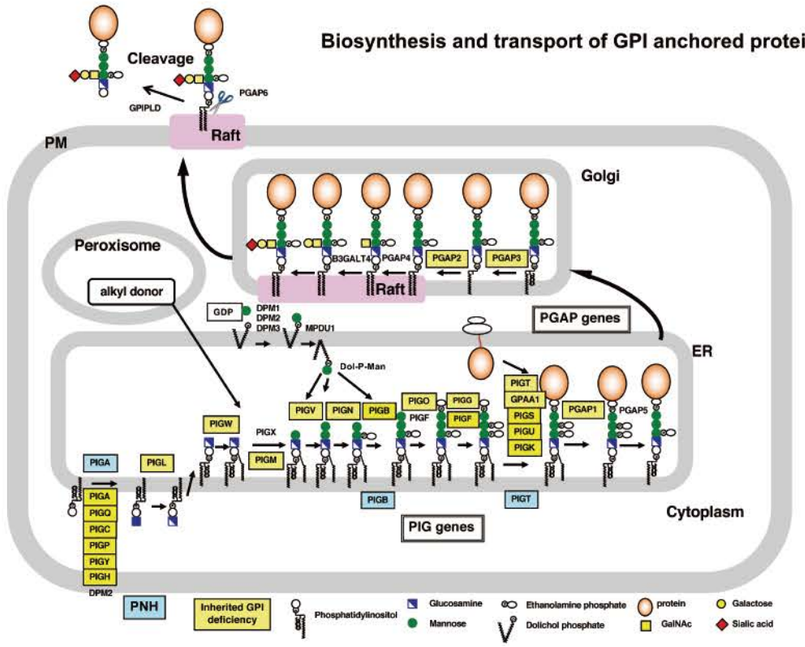
●How are GPI-anchored proteins (GPI-APs) regulated?

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

●Molecular mechanisms of GPI deficiencies.

We found that paroxysmal nocturnal hemoglobinuria (PNH) is caused by somatic mutation of the X-linked PIGA gene, a gene for GPI-anchor biosynthesis. Recently, we reported four cases of the atypical PNH caused by the somatic microdeletion of one allele of the PIGT gene in combination with a germline mutation in the other allele. These patients showed autoinflammatory symptoms in addition to the common symptoms of PIGA-PNH. We are now accumulating similar cases.

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



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

DEPT. OF MALARIA VACCINE DEVELOPMENT

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

Toshihiro Horii

Endowed Chair Professor

Dr. Horii received his Ph.D. from Osaka University in 1981. After working at the Faculty of Science in Osaka University as Research Associate, he was appointed Associate Professor at RIMD in 1991 and promoted to Professor in 1999. He moved to the current department in 2019.

STAFF

SA Prof. :
Nirianne Palacpac Marie Querijero

Publication

(1) First-in-human randomized trial and follow-up study of Plasmodium falciparum blood-stage malaria vaccine BK-SE36 with CpG-ODN(K3) Ezoe S. et al., ***Vaccine*** (2020), S0264-410X(20)31227-5 doi: 10.1016/j.vaccine.2020.09.056

(2) Molecular Camouflage of Plasmodium falciparum Merozoites by Binding of Host Vitronectin to P47 Fragment of SERA5. Tougan T., et al. ***Sci Rep.*** (2018) 8:5052. doi: (5)10.1038/s41598-018-23194-9.

(3) 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.

(4) 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:e98460. doi: 10.1371/journal.pone.0098460.

(5) Phase 1b randomized trial and follow-up study in Uganda of the blood-stage malaria vaccine candidate BK-SE36. Palacpac N.M.Q., et al., ***PLoS One.*** (2013) 8: e64073. doi:10.1371/journal.pone.0064073

(6) Plasmodium falciparum serine repeat antigen 5 (SE36) as a malaria vaccine candidate. Palacpac N.M., et al., ***Vaccine.*** (2011) 29:5837-45. doi: 10.1016/j.vaccine.2011.06.052.

(7) Evidences of Protection Against Blood-stage Infection of Plasmodium falciparum by the Novel Protein Vaccine SE36. Horii T., et al., ***Parasitol. Int.*** (2010) 59:380-6. doi: 10.1016/j.parint.2010.05.002.

●Malaria vaccine targeting SERA

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 and developing malaria vaccine NPC-SE36 by utilizing a recombinant SE36 protein. Epidemiological studies in malaria hyper-endemic areas showed that children with antibodies against SE36 experienced few or no symptomatic/clinical malaria, albeit such children are a minority.

It was surprising that Ugandan adults that suffered numerous malaria infections did not respond to vaccination with NPC-SE36. By contrast, malaria-naive Japanese adults produced high levels of antibodies. Moreover, in young Ugandan children that experienced few malaria episode, we observed good antibody response. We obtained 72 % protective efficacy 1 year post-2nd-vaccination in a follow-up study of 6-20 years old in the phase Ib trial. We have conducted Phase Ib clinical trial of NPC-SE36 in Burkina Faso in west Africa in 2015-2017. Vaccine was well tolerated, and it was found that the immune response in 1 year infants group was much higher than children 2-5 years old. We have also completed Phase Ib clinical trial (adult to 1 year baby) of NPC-SE36 with CpG adjuvant that stimulates innate immunity resulting in a significant immune response without safety concern. Phase II clinical trial is under planning.

●Molecular strategy for malaria parasite survival and a function of SE36 protein

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, SE36 is highly homologous among malaria parasites worldwide. Recently we have shown that SE36 protein tightly binds to host vitronectin as cytoadherence molecule on the surface of parasite cell, merozoite, and vitronectin further binds to over 30 different host proteins for molecular camouflage from host immune system. Presentation of SE36/vitronectin complex to host immune system by repeated infections may cause immune tolerance against SE36 protein. Thus lower immune response may result in a limited genetic polymorphism of SE36.

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

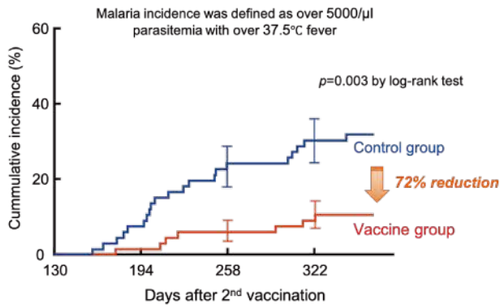


Fig. 2. Protective efficacy of NPC-SE36 malaria vaccine
Palacpac et al., Plos ONE. 2013; 8(5): e64073

DEPT. OF CELLULAR IMMUNOLOGY

Cellular Immunity by T cells play important roles for cancer, infectious diseases, allergy, and autoimmune diseases. Therefore, T cells are good medical target. Appropriate induction or reduction of T cells help to overcome and control these diseases. In our laboratory, we are developing new drug and technology which utilize built-in mechanisms of T cell response induction in our body, especially from the point of views of adjuvant, antigen presenting cells, and T cell epitopes.

Taiki Aoshi

Endowed Chair
Associate Professor

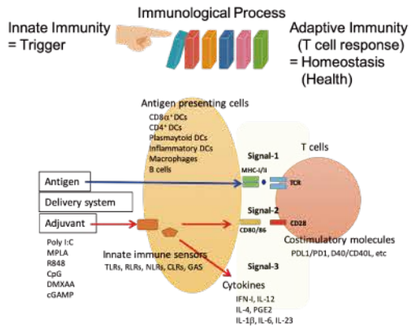
Dr. Aoshi received his M.D. from Hamamatsu University School of Medicine in 1999 and his Ph.D. from the same institution in 2006. He was appointed as SA Associate Professor of BIKEN Innovative Vaccine Research Alliance Laboratories at RIMD in 2015 after working at Washington University in St. Louis, NIBIOHN, and IFReC in Osaka University. He took his current position in 2020.

STAFF

Endowed Chair Assistant Professor :
Yumi Katayama

Effective induction of T cell responses needs appropriate sequential immunological processes including 1) innate immune response induction by adjuvant, antigen uptake and processing by antigen presenting cells, and effector T cell activation by recognizing peptides (T cell epitope) bound on MHC molecules. However, the details of these sophisticated and complexed immunological processes are still not fully understood yet.

We are trying to understand the details of T cell response induction processes from the initial innate immunity to final adaptive immunity. We believe our research provide critical information to utilize built-in cellular immunity mechanisms in our body for real medicine. Controlling and adjusting the T cell responses depending on the conditions and diseases (like cancer) will provide very effective but gentle treatment and help medical health promotions.



Publication

(1) Microfluidic-prepared DOTAP nanoparticles induce strong T-cell responses in mice. Haseda Y., et al. ***PLoS One.*** (2020) 15(1):e0227891.

(2) Lipid nanoparticles of Type-A CpG D35 suppress tumor growth by changing tumor immune-microenvironment and activate CD8 T cells in mice. Munakata L., et al. ***J Control Release.*** (2019) 313:106-119.

(3) Development of Nonaggregating Poly-A Tailed Immunostimulatory A/D Type CpG Oligodeoxynucleotides Applicable for Clinical Use. Aoshi T., et al. ***J Immunol Res.*** (2015) 316364.

(4) Bacterial entry to the splenic white pulp initiates antigen presentation to CD8+ T cells. Aoshi T., et al. ***Immunity.*** (2008) 29 (3):476-86.

THAILAND-JAPAN RESEARCH COLLABORATION CENTER

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 fourth phase (2020-2025) 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 upon the emergence of such a disease, 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.

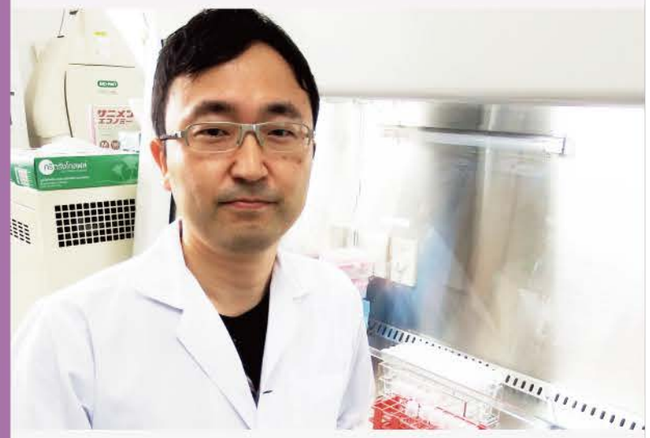
BSL-2 and BLS-3 laboratories in the center.

SECTION OF BACTERIAL INFECTIONS

Tetsuya Iida (concur.)
Professor

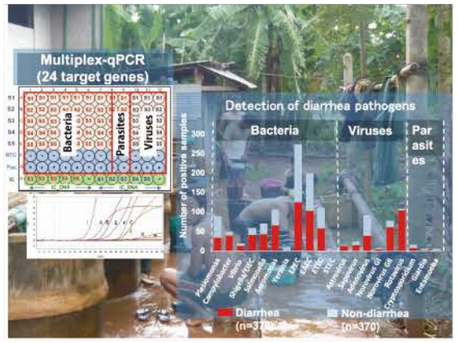
Kazuhisa Okada
SA Associate Professor

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.



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.



Detection of "pathogenic" agents from stool specimens of inpatients, with acute diarrhea and control subjects using multiplex real-time PCR. Eight hospitals in different parts of Thailand participate in this study.

Publication

(1) Etiologic features of diarrheagenic microbes in stool specimens from patients with acute diarrhea in Thailand. Okada K. et al., ***Sci. Rep.*** (2020) 10:4009.

(2) Simultaneous detection and quantification of 19 diarrhea-related pathogens with a quantitative real-time PCR panel assay. Wongboot W. et al., ***J Microbiol Methods.*** (2018) 151:76-82

(3) Vibrio cholerae embraces two major evolutionary traits as revealed by targeted gene sequencing. Okada K., et al. ***Sci. Rep.*** (2018) 8(1):1631

(4) Characterization of 3 Megabase-Sized Circular Replicons from Vibrio cholerae. Okada K., et al. ***Emerg Infect Dis.*** (2015) 21(7):1262-3.

(5) Cholera in Yangon, Myanmar, 2012-2013. Aung WW., et al. ***Emerg Infect Dis.*** (2015) 21(3):543-4.

(6) Vibrio cholerae O1 isolate with novel genetic background, Thailand--Myanmar. Okada K., et al. ***Emerg Infect Dis.*** (2013) 19:1015-7.

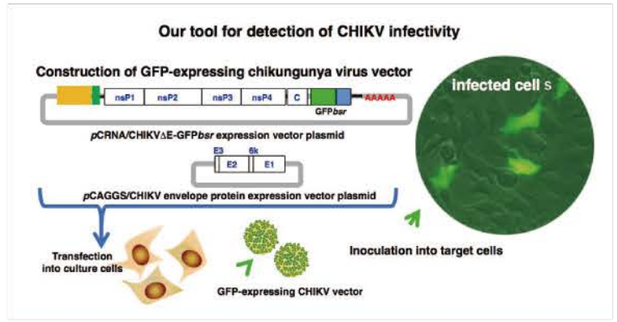
SECTION OF VIRAL INFECTIONS

STAFF

Head, Prof. :
Takeshi Kobayashi (concur.)
SA Assoc. Prof. :
Hiroto Mizushima
SA Assoc. Prof :
Atsushi Yamanaka

A variety of mosquito-borne viral infections are widespread in Thailand located in the tropics. Mosquito-borne viruses may spread to countries around the world, including Japan, which has strong diplomatic relations with Thailand. Therefore, establishment of countermeasures against infection of mosquito-borne viruses based on basic research is important issue in endemic prevention. Among mosquito-borne viruses distributed in Thailand, we are analyzing the process of infection of chikungunya virus, which is the causative agent of chikungunya fever, using molecular biological and immunological methods. In addition, we will start basic research on anti-dengue virus antibodies with the aim of developing a vaccine against dengue viruses, which is the causative agent of dengue fever.

Acute gastroenteritis caused by norovirus infection, which is observed all over the world every year, is one of the problems in public health. Viral diversification due to mutations and recombination of viral genome is thought to enable evasion from host immunity and persistent prevalence. However, it is not fully understood how viruses diversify and how they are retained in human community. Based on epidemiological surveys, we are conducting research with the aim of understanding changes in epidemic strains associated with genomic mutation and elucidating the life cycle of norovirus.



Publication

(1) Identification of GII.14[P7] norovirus and its genomic mutations from a case of long-term infection in a post-symptomatic individual. Nonthabenjawan N et al., ***Infect. Genet. Evol.*** 86:104612 (2020).

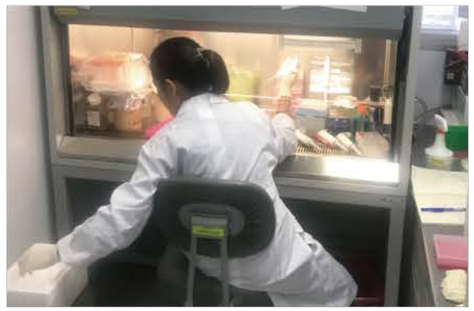
(2) Norovirus transmission mediated by asymptomatic family members in households. Phattanawiboon B et al., ***PLoS One*** 15(7):e0236502 (2020).

(3) Anti-chikungunya virus antibody that inhibits viral fusion and release. Tumokosit U et al., ***J. Virol.*** 94(19):e00252-20 (2020).

(4) The use of green fluorescent protein-tagged virus-like particles as a tracer in the early phase of chikungunya infection. Tumokosit U et al., ***Virus Res.*** 272:197732 (2019).

(5) The dynamics of norovirus genotypes and genetic analysis of a novel recombinant GII.P12-GII.3 among infants and children in Bangkok, Thailand between 2014 and 2016. Boonchan M et al., ***Infect. Genet. Evol.*** 60:133-139 (2018).

Evaluation of virus replication using cultured cell



Detection of virus contained in patient-derived specimens

SECTION OF BACTERIAL DRUG RESISTANCE RESEARCH

Tetsuya Iida

Professor

Dr. Iida graduated Faculty of Science, Kyoto University in 1984 and 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.

STAFF

Assoc. Prof. : Yukihiro Akeda (concur.) ／
SA Assoc. Prof. : Yo Sugahara ／
Asst. Prof. : Dan Takeuchi

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

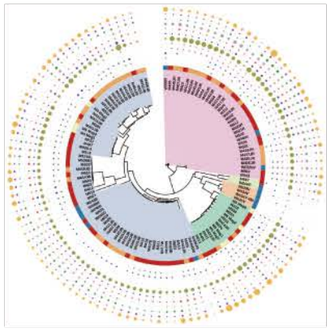


Figure. A whole genome SNP-based phylogenetic tree of CRE isolates from Myanmar. The inner colored regions define bacterial species. Next outer colored regions denote the origins of isolates. Colors and sizes of outer dots denote classes and numbers of antimicrobial resistance genes harbored by each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

Publication

(1) *In Vitro* Efficacy of Meropenem-Cefmetazole Combination Therapy against New Delhi Metallo-β-lactamase-producing *Enterobacteriaceae*. Hagiya H, et. al. ***Int J Antimicrob Agents.*** (2020) 55:105905.

(2) Genomic characterization of an emerging *bla*KPC-2 carrying *Enterobacteriaceae* clinical isolates in Thailand. Kerdsin A, et. al. ***Sci Rep.*** (2019) 9:18521.

(3) Genomic characterisation of a novel plasmid carrying *bla*IMP-6 of carbapenem-resistant *Klebsiella pneumoniae* isolated in Osaka, Japan. Abe R et. al. ***J Glob Antimicrob Resist.*** (2019) pii: S2213-7165(19)30257-7.

(4) Dissemination of carbapenemase-producing *Enterobacteriaceae* harbouring *bla*NDM or *bla*IMI in local market foods of Yangon, Myanmar. Sugawara Y, et. al. ***Sci Rep.*** (2019) 9:14455.

(5) Rapid screening and early precautions for carbapenem-resistant Acinetobacter baumannii carriers decreased nosocomial transmission in hospital settings: a quasi-experimental study. Yamamoto N, et. al. ***Antimicrob Resist Infect Control.*** (2019) 8:110.

SECTION OF ANTIVIRAL RESEARCH

Tatsuo Shioda (concur.)

Professor

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.

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.

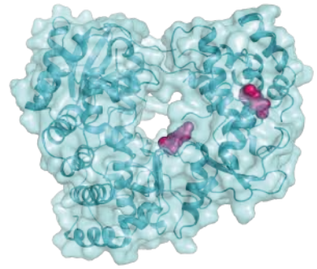


Figure: Structure of RNA-dependent RNA polymerase (blue) and its inhibitor RK-0404678 (red)

Publication

(1) Promising application of monoclonal antibody against chikungunya virus E1- antigen across genotypes in immunochromatographic rapid diagnostic tests. Suzuki K., et al., ***Virol J.*** (2020) 17(1): 90.

(2) Discovery of a small molecule inhibitor targeting dengue virus NS5 RNA-dependent RNA polymerase. Shimizu H. et al., ***PLoS Negl Trop Dis.*** (2019) 13 (11):e0007894.

(3) Evaluation of novel rapid detection kits for dengue virus NS1 antigen in Dhaka, Bangladesh, in 2017. Suzuki K. et al., ***Virol J.*** (2019) 16(1):102.

(4) Broad-spectrum monoclonal antibodies against chikungunya virus structural proteins: Promising candidates for antibody-based rapid diagnostic test development. Tuekprakhon A. et al., ***PLoS One.*** (2018) 13(12):e0208851

(5) Evaluation of an immunochromatography rapid diagnosis kit for detection of chikungunya virus antigen in India, a dengue-endemic country. Jain J. et al., ***Virol J.*** (2018) 15(1):84.

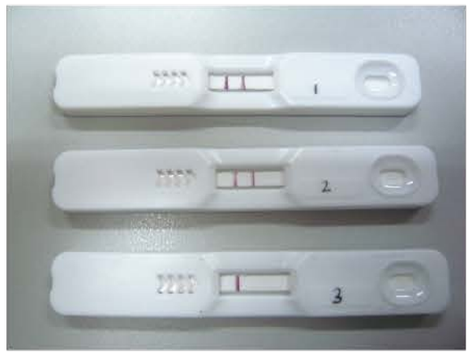
(6) Variation at position 350 in the Chikungunya virus 6K-E1 protein determines the sensitivity of detection in a rapid E1-antigen test. Tuekprakhon A. et al., ***Sci Rep.*** (2018) 8(1):1094.

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, Prof. :
Tatsuo Shioda (concur.)



Diagnostic kit developed by the MOCID.

Publication

(1) Dengue virus susceptibility in novel immortalized myeloid cells. Yamanaka A., et al., ***Heliyon*** (2020) 6 e05407

(2) Intraperitoneal injection with dengue virus type 1-infected K562 cells results in complete fatality among immunocompetent mice. Yamanaka A. et al., ***Antiviral Res.*** (2019) 170:104560.

(3) Key Amino Acid Substitution for Infection-Enhancing Activity-Free Designer Dengue Vaccines. Yamanaka A et al., ***iScience.*** (2019) 13:125-137

(4) High-throughput neutralization assay for multiple flaviviruses based on single-round infectious particles using dengue virus type 1 reporter replicon. Matsuda M. et al., ***Sci Rep.*** (2018) 8(1):16624.

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

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

Column

HOW WE TACKLE COVID-19

The first signs of the COVID-19 pandemic emerged at the end of 2019 and has since become an urgent global health issue. Given the scale of this threat and the role of the Research Institute for Microbial Diseases as a research hub for infectious diseases, we have been promoting the following research initiatives:

Established our COVID-19 R&D team, whose aim was to develop effective and practical research questions and projects via vigorous information exchange between various fields of study.

The Department of Genome Informatics offered expanded support for 2019-nCoV sequence analysis.
▷ ***https://sysimm.org/news/2019-ncov-japanese***

Organized a vaccine R&D group, collaborating with the Research Foundation for Microbial Diseases of Osaka University (BIKEN Foundation) and the National Institutes of Biomedical Innovation, Health and Nutrition. This project has since been adopted as a 2020 AMED'S CiCLE project, promoting industry-academia-government collaboration.

Created a research group specializing in various emerging infectious diseases. This group consists of experts from various fields, including virology, bacteriology and parasitology.

We expanded our offer of support to help with the analysis of SARS-CoV-2 at other research institutions.

Launched an outreach webpage for COVID-19 and SARS-CoV-2 on our official website, which has subsequently matured into its own website, launched March 2021.
▷ ***https://biken.yawaraka-scienece.com***

Enlarged (10^6 times) model of SARS virus

BSL-3 laboratory at the Central Laboratory for Biological Hazardous Microbes

Animal experiments can be completed under BSL-3 conditions.

ANIMAL RESOURCE CENTER FOR INFECTIOUS DISEASES

To study infectious diseases, immunological responses, 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 two areas: SPF (specific pathogen free) and BSL3 (biosafety level 3). The condition of the animals is monitored regularly. Before gaining access to restricted areas, researchers must take an official orientation and all the animal experiments have to be approved by the Institutional Animal Care and Use Committee. We follow the 3Rs (Replacement, Reduction, Refinement) and the five freedoms for animals.

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. For more information about our research and services, please visit our homepage (https://arcid.biken.osaka-u.ac.jp/).

STAFF

Head, Prof. : Masahito Ikawa ／
Assoc. Prof. : Haruhiko Miyata (concur.) ／
Assoc. Prof. : Norikazu Yabuta ／
Asst. Prof. : Keisuke Shimada ／
Asst. Prof. : Chihiro Emori (concur.) ／
SA Asst. Prof. : Tsutomu Endo (concur.) ／

Table 1 *Tg, transgenic; KO, knockout; IVF, in vitro fertilization; ET, embryo transfer.

	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*
2016-2018	505	21	191*

* 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 (left, built in 2019, four-story).
Building C (right, built in 2009, four-story).

OFFICE FOR RESEARCH PROMOTION

The researchers at RIMD are supported by administrative functions provided by the Office for Research Promotion. The aim of this office is to promote communication among researchers and to develop human resources with expertise in scientific research. The office also communicates RIMD research achievements to the general public.

STAFF

Head, Prof. : Nobuyuki Takakura (concur.) ／
Assoc. Prof. : Ryo Iwamoto ／
SA Assoc. Prof. : Saya Nakagomi (concur.)

Lecture Program

Program for Undergraduate Students

Graduate Program for Advanced Interdisciplinary Studies
"Combined Program on Microbiology and Immunology"

Seminars and Symposia

Biken Monthly Seminar

Advanced Seminar Series
The researchers invited from other institutes will give the seminars on the current expertise in the field of immunology and microbiology.

Awaji International Forum on Infection and Immunity
In the symposiums, leading scientists in the areas of bacteriology, immunology, parasitology, and virology from abroad and Japan present the cutting-edge of the ecent results and freely discuss in the relaxed environment of the Awaji Island.

International Symposium of the Institute Network for Biomedical Sciences
International Symposium of The Institute Network

RIMD/IFReC Orientation

Orientation and Lab Tour for RIMD and IFReC for candidates of graduate schools/postdoctoral positions.

Public communications and outreach

This Office works for providing accurate information about our discoveries.
・RIMD website and SNS management
・Publishing RIMD booklets, newspapers
・Organizing Outreach Events

Institutional Research

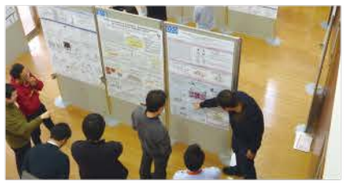
By archiving our research data and activities, we try to evaluate the institute's achievements.

Taniguchi Scholarship: International Students Scholarship Program

A scholarship program for students from ASEAN countries to study a RIMD as graduate students and provide leadership and support to become independent researchers.

Awaji International Forum on Infection and Immunity

Advanced Seminar Series



Poster session in RIMD Result Presentation

RIMD Result Presentation Academic prize awardee

Winterschool for High school teachers

RIMD booklets and newsletters

CENTRAL INSTRUMENTATION LABORATORY

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.

STAFF

Head, Prof. : Hiroaki Miki (concur.) ／
Assoc. Prof. : Shinji Higashiyama ／
Assoc. Prof. : Naohisa Goto ／
Asst. Prof. : Fuminori Sugihara

Central Instrumentation Laboratory staffs

RADIOISOTOPE LABOLATORY

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, 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.

STAFF

Head, Prof. : Hiroaki Miki (concur.)

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 m2 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.

STAFF

Head, Prof. : Tatsuo Shioda (concur.)

ADMINISTRATION

General Affairs Section ／
Accounting Section ／
Research Cooperation Section

BIKEN INNOVATIVE VACCINE RESEARCH ALLIANCE LABORATORIES

As the recent Ebola virus outbreak in Africa and the worldwide 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.

Director, Prof. :
Takeshi Kobayashi (concur.)

Experimental laboratories.

VACCINE CREATION GROUP

Yasuo Yoshioka

SA Professor

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) Murine cross-reactive non-neutralizing polyclonal IgG1 antibodies induced by influenza vaccine inhibit the cross-protective effect of IgG2 against heterologous virus in mice. Shibuya M et al. ***J Virol.***(2020) pii: JVI.00323-20.

(2) Carbonate Apatite Nanoparticles Act as Potent Vaccine Adjuvant Delivery Vehicles by Enhancing Cytokine Production Induced by Encapsulated Cytosine-Phosphate-Guanine Oligodeoxynucleotides. Takahashi H, et al. ***Front Immunol.*** (2018) Apr 18;9:783.

(3) 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.

(4) 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.

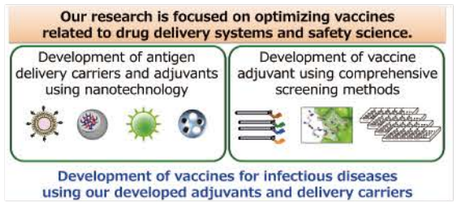
(5) Silica and titanium dioxide nanoparticles cause pregnancy complications in mice. Yamashita K, Yoshioka Y, et al. ***Nat Nanotechnol.*** (2011) 6 (5):321-8.

STAFF

SA Assoc. Prof. : Toshiro Hirai ／
Undergrad. Student 3 ／ Grad. Student 7

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.



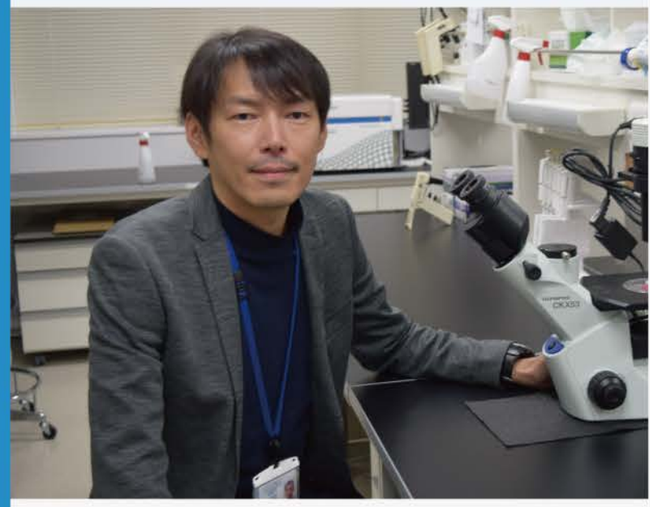
VIRUS VACCINE GROUP

It is difficult to develop vaccines against pathogens that cannot be suppressed by antibody-mediated immunity alone, pathogens that cannot be cultured, or those whose infection is difficult to evaluate due to the absence of animal models. The Viral Vaccine Project is conducting virus research with the aim of developing here in Japan, the world's first vaccines targeting these infectious diseases.

Hirotaka Ebina

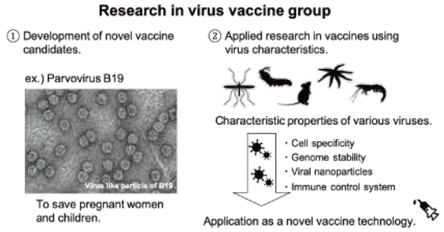
SA Assoc. Professor

Dr. Ebina obtained his Ph.D. from Tohoku University in 2004. After working at the National Insitute of Health, USA and the Institute for Virus Research, Kyoto University, he joined the Research Foundation for Microbial Diseases of Osaka University in 2016. He was appointed current position in 2020.



Human parvovirus B19 infection in pregnant women causes Hydrops fetalis due to severe fetal anemia. Therefore, vaccines are needed but have not yet been developed. However, no virus culture method has been established, the virus host is limited to humans, and there is no adequate animal model available. We are developing novel parvovirus vaccines using various approaches, such as analyzing parvovirus replication mechanism and performing human epidemiological research.

Viruses that replicate in a variety of organisms, not only humans, have unique properties that can be applied as vaccines for humans. We are conducting virus research with the aim of creating powerful, safe and novel vaccine platforms by taking advantage of the characteristics of various viruses.



Publication

(1) Live attenuated SARS-CoV-2 vaccine candidate: Protective immunity without serious lung lesions in Syrian hamsters. Okamura S. et al. ***bioRxiv*** (2021) doi: https://doi.org/10.1101/2021.02.15.430863

(2) Quantification of a cell-mediated immune response against varicella zoster virus by assessing responder CD4high memory cell proliferation in activated whole blood cultures Haredy AM., et al. ***Vaccine*** (2019) 37 (36):5225-5232.

(3) Harnessing the CRISPR/Cas9 system to disrupt latent HIV-1 provirus. Ebina H., et al. ***Scientific Reports*** (2013) 3:2510.

(4) Integrase-independent HIV-1 infection is augmented under conditions of DNA damage and produces a viral reservoir. Ebina H., et al. ***Virology*** (2012) 427 (1):44-50.

Column

RESEARCH INSTITUTE FOR MICROBIAL DISEASES AND VACCINE DEVELOPMENT

The Institute for Microbiological Diseases (RIMD) and the Research Foundation for Microbial Diseases of Osaka University (BIKEN Foundation), were established at the same time in 1934. RIMD was established to engage in academic research on infectious diseases. The BIKEN Foundation was launched for manufacturing and development of vaccines based on the RIMD research. Their cooperative relationship is continuing until now and they established the collaborative laboratory for research and development of novel vaccines for the next generation.

Research Institute for Microbial Diseases

To undertake basic research in microbiology and immunology

The Research Foundation for Microbial Diseases of Osaka University

To undertake vaccine development and manufacturing vaccine, based on the RIMD research

Developed vaccines by Research Institute for Microbial Diseases

Developed a measles vaccine

Okuno succeeded at the same time with Dr. Enders (USA) to isolate the measles virus. He developed the world's first vaccine using SPF (Specific Pathogen Free) chicken egg based manufacturing process. This process is still in use.

Developed a chickenpox vaccine

The chickenpox vaccine he developed, "OKA strain" , is still in use all over the world. Currently in Japan, the vaccine is manufactured by the BIKEN Foundation. Mitsubishi Tanabe Pharma and Takeda Pharmaceutical Company sell them.

Now, we are trying to develop novel vaccines with high safety and efficacy.

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.

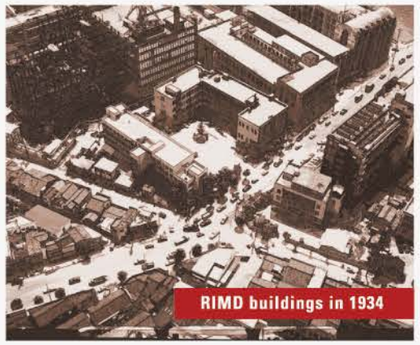
KEY PERSON

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.

Gendo Yamaguchi

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.



RIMD buildings in 1934

RIMD History

HISTORY

1934
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).

RIMD buildings in 1934

The Takeo Tuberculosis research Center

The main RIMD building at Dojima in 1934

The Osaka Leprosy Institute

1967
RIMD moved to the Suita Campus

RIMD buildings in 1967

The Suita Campus, Osaka University

1980s
Developed a chickenpox vaccine
Michiaki Takahashi

2000s
Elucidation of the Innate Immune System
Shizuo Akira

2005
Three centers for specialized research on infectious disease and genome information launched. The Research Collaboration Center on Emerging and Re-emerging Infections in Thailand was founded

2008
Selected for funding by the Global COE programs on the theme of "Frontier Biomedical Science Underlying Organelle Network Biology"

2015
BIKEN Innovative Vaccine Research Alliance Laboratories was launched

KEY PERSON

1950s
Discovered Vibrio parahaemolyticus
Tsunesaburo Fujino

1960s
Discovered cell fusion
Yoshio Okada

Developed a measles vaccine
Yoshiomi Okuno

1970s
Discovered a viral oncogene
Kumao Toyoshima

1993
RIMD Hospital was merged with Osaka University Hospital

2003
Selected for funding by the 21st Century COE programs on the theme of "Combined program on microbiology and immunology"

2007
Immunology Frontier Research Center (IFReC) was founded

2008
Approved as a Joint Usage / Research Center by Ministry of Education, Culture, Sports, Science and Technology

The Epochs in Biology

HISTORY

1798
Development of Smallpox vaccine (The first successful vaccine developed)
E. Jenner

1870-1880
Establishment of the germ theory of disease
L. Pasteur, R. Koch

1919
Proved chemical carcinogenesis
K. Yamagiwa

1928
Discovery of Penicillin (The first antibiotics)
A. Fleming

1953
Discovery of the DNA structure
J. Watoson, F. Crick

1957
Clonal selection theory in immunology
F.M. Burnet

1965
Revealed Genetic code
H. Khorana

1975
Production of monoclonal antibodies using cell fusion technique.
C. Milstein

1977
Discovery of the genetic mechanism to produce antibody diversity
S. Tonegawa

1979
Discovery of oncogene, c-Src
J.M. Bishop, H.E. Varmus

1980
Eradication of smallpox was declared by WHO

1981
Establishment of Embryonic Stem Cells (ES cells)
M. Evans, M. Kaufman

1996
Dolly the sheep was born (The first cloned mammal)

2003
Human Genome Project completed

2006
Establishment of Induced Pluripotent Stem Cells (iPS cells)
S. Yamanaka

RIMD AWARDS

2020

FY2019 Outcome Presentation, Grant-in-Aid for Scientific Research on Innovative Areas - Platforms for Advanced Technologies and Research Resources, Best Presentation Award

Masahiro Wakita　Dept. of Molecular Microbiology　2020.2

Kuroya Award, Japanese Society for Bacteriology

Shigeaki Matsuda　Dept. of Bacterial Infections　2020.2

The 93rd Annual Meeting of Japanese Society for Bacteriology Excellent Presentation Award

Ken Uemura　Dept. of Molecular Microbiology　2020.2

The 93rd Annual Meeting of Japanese Society for Bacteriology Excellent Presentation Award

Dendi Krisna Nugraha　Dept. of Molecular Bacteriology　2020.2

Osaka University Female Graduate Student Research Excellent Award

Dhira Saraswati Anggramukti　Dept. of Bacterial Infections　2020.3

The Commendation by the Minister of Education, Culture, Sports, Science and Technology, The Young Scientists' Prize

Shimpei Kawamoto　Dept. of Molecular Microbiology　2020.4

The Nagase Scientific Promotion Award

Tohru Ishitani　Dept. of Homeostatic Regulation　2020.4

The Japanese Society of Parasitology, The 67th Koizumi Prize

Masahiro Yamamoto　Dept. of Immunoparasitology　2020.5

Tokyo University of Science, The 3rd Butsuri Gakuen Prize

Eiji Hara　Dept. of Molecular Microbiology　2020.6

The Kao Research Initiative Award 2020

Yuki Akieda　Dept. of Homeostatic Regulation　2020.6

JST Award for Academic Startups 2020, MEXT Minister's Award

Shota Nakamura　Laboratory of Pathogen Detection and Identification　2020.9

IVBM2021E-poster awards (The most 'Liked' E-poster by participants)

Yumiko Hayashi　Dept. of Signal Transduction　2020.9

The 63rd Hideyo Noguchi Memorial Prize 2020

Hisashi Arase　Dept. of Immunochemistry　2020.9

The 2020-2021 Osaka University Prize

Haruhiko Miyata　Dept. of Experimental Genome Research　2020.11

The 50th Princess Takamatsu Cancer Research Fund Prizes

Eiji Hara　Dept. of Molecular Microbiology　2020.12

Shimpei Kawamoto
Dept. of Molecular Microbiology


Masahiro Yamamoto
Dept. of Immunoparasitology


Haruhiko Miyata
Dept. of Experimental Genome Research

2020

COLLABORATION WITH RELEVANT INSTITUTES AND UNIVERSITIES

MEXT 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. We provide specialized facilities equipped with BSL2 and 3 laboratories in Animal Resource Center and Infectious Diseases and Central Laboratory for Biological Hazardous Microbes. In addition, Genome Information Center is for genome research with Next Generation Sequencers and support researchers to analyze genomes of organisms.

We also hosts international symposiums such as Awaji International Forum on Infection and Immunity to share research achievements and facilitate communication among researchers.

Animal Facility

Next Generation Sequencer and server

Awaji International Forum on Infection and Immunity

International Collaborations

RIMD researchers conduct international collaborative Projects that involve researchers from various contries. FIMD also concludes academic agreements with four institutes and universities.

Academic agreements

Country	Institute / University	Starting date
Thailand	Bamrasnaradura Infectious Diseases Institute	2013/2/15
U. S. A.	Center for Drug Discovery, Baylor College of Medicine	2017/4/15
Lithuania	Vilnius University (Faculty of Medicine)	2018/2/15
Bangladesh	Apollo Hospitals Dhaka	2018/5/13
Germany	University of Bon	2018/11/5
Vietnam	National Hospital for Tropical Diseases in Hanoi, Vietnam	2019/7/29

Collaboration with BIKEN foundation and Immunology Frontier Research Center (IFReC)

RIMD and IFReC conducts world-class researches in biological fields including microbiology and immunology. RIMD and IFReC collaborate each other to promote researches and foster talented human resources in these fields. The BIKEN foundation develops vaccines, thereby to translate the research achievements in of RIMD to the society. In addition, the foundation is dedicated to promote basic research through the Taniguchi Memorial Scholarship program and the BIKEN Center for Innovative Vaccine Research Alliance Laboratories.

The Research Foundation for Microbial Diseases of Osaka University

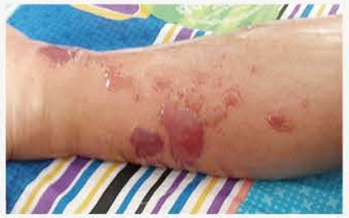
TO DEVELOP HUMAN RESOURCES GLOBALLY

● Clinical Training Course on Tropical Infectious Diseases in the Thailand

The age of global tourism means that people can spread pathogens worldwide though the traveling. Infectious diseases are now a global problem that extends beyond national borders. In Japan, there is a compelling need for experienced specialists for 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 staffs operating in a highly endemic area. Approximately 100 doctors participated in this training course, and the alumni are conducting basic/clinical research for infectious diseases or working for global health in various governmental organizations and NGOs.

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

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>

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

Udon Thani :
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

Taniguchi Scholarship: International Students Scholarship Program

RIMD established a scholarship program for Students from ASEAN countries to study at RIMD as graduate students and provide leadership and support to become independent researchers. Particularly excellent candidates will be offered a regular faculty position at RIMD after they obtained Ph.D.. This new scholarship program aims to significantly contribute to the development of science by training world-leading researchers from the international students learned at RIMD.

Seminars and Events

We organize conferences and seminars to facilitate communication among researchers. We also organize an outreach event to provide accurate information about our research findings and achievements.

● Events for Researches

International Conferences

Awaji International Forum on
Infection and Immunity
(http://awaji-forum.com/)

International Symposium of the
Institute Network
(http://square.umin.ac.jp/network/)

Awaji International Forum on Infection and Immunity

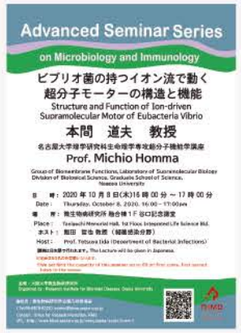
BIKEN Monthly Seminar

Held monthly, except August and December. Young researchers present their recent research findings.

Advanced Seminar Series on Microbiology and Immunology

Lecture series hosted by the Office for Research Promotion. Leading researchers in the field of Microbiology and Immunology are invited to this lecture series.

Biken Monthly Seminar



Advanced Seminar Series

Bridge Seminar

Seminar series hosted by young researchers at RIMD.

● Outreach Events

We organize outreach Events and Exhibitions for the non-scientific community. In addition, we try to encourage young students, including high school students and junior high school students, to take an interest in scientific research.

Osaka University ICHO Festival

Online seminar

For Students and Researchers who want 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.

www.biken.osaka-u.ac.jp/en/recruit/

Information in Osaka University website

Study at Osaka University

> Osaka University website for Global Affairs
https://www.osaka-u.ac.jp/en/international

> Study Abroad at Osaka University
https://www.osaka-u.ac.jp/sp/whyou/

Student Support

> Center for International Education and Exchange(CIEE)
https://ciee.osaka-u.ac.jp/

> Support Office for International Students and Scholars
https://iss-intl.osaka-u.ac.jp/supportoffice/

International Students Groups

> Osaka University International Students Association (OUISA)
https://ouisa.info/

Work at Osaka University

> IFReC Website for Overseas Researchers
http://www.ifrec.osaka-u.ac.jp/en/liaison/

Information in Japanese Government or Organization

Visa

> Immigration Services Agency of Japan
https://www.isa.go.jp/en/index.html

> Websites of Japanese Embassies in your country
https://www.mofa.go.jp/about/emb_cons/mofaserv.html

Scholarship

> Japan Student Services Organization (JASSO)

> Study in Japan
https://www.studyinjapan.go.jp/en/

> Scholarship for International Students in Japan
https://www.studyinjapan.go.jp/en/planning/by-style/pamphlet/

> Japanese Government (MEXT) Scholarship Students
https://www.studyinjapan.go.jp/en/planning/scholarship/

Municipal Groups for International Exchange

> Suita International Friendship Association
https://suita-sifa.org/en/

> Minoh Association For Global Awareness
https://mafga.or.jp/en/

> Association for Toyonaka Multicultural Symbiosis
https://www.a-atoms.info/information-for-foreigners/

> Osaka Foundation of International Exchange, Planning and Promotion Group
https://www.ofix.or.jp/english/

Grad Students Studying in RIMD

INTERVIEW 01

Why RIMD

The curiosity I always wonder about the nature of life brings my life path across the research work since I was in senior high school. My path to RIMD began in 2017 when I was at the end of my master's degree and working at the Institute of Tropical Disease Center, Airlangga University, Indonesia. The director informed me that RIMD was looking for potential candidates to study and conduct research at Osaka University. When I heard about this opportunity at RIMD, I was instantly reminded that the first CRISPR sequences were identified at RIMD. The research activities carried out at RIMD are outstanding, making this institution one of the leading research centers for microbiology and immunology; making it an obvious choice for my Ph.D. studies.

A Day in the Life

I spend most of my days doing research. Facing a lot of research articles and experiments have become a habit in research. Trying to solve puzzling problems in research is complicating yet challenging. Fortunately, I have a great mentor who is always supporting, teaching, and directing me in the lab. Outside of the lab, I spend my time enjoying Japan sightseeing spots and cuisines. In addition, as an Indonesian in Japan, I enjoy Indonesian Student Association, which organizes a lot of events and makes living in Japan still feel like home.

Andre Pratama

Department of Bacterial Infections
Doctoral course in Graduate School of Frontier Biosciences

BSc: Faculty of Science and Technology, Airlangga University, Indonesia
MSc: Faculty of Science and Technology, Airlangga University, Indonesia

Research Interest

Having a background as a chemist, I am always excited to work with biochemical and molecular biology approaches to the bacterial world. Fortunately, I joined Prof. Tetsuya Iida's group to study an important marine pathogen discovered in RIMD, *Vibrio parahaemolyticus*, to understand the Type 3 Secretion System (T3SS) regulation. This remarkable system is used as a weapon by this bacterium to deliver virulence proteins into host cells and induce disease. Our lab previously found that *V. parahaemolyticus* has two different T3SSs that are responsible for cytotoxicity and enterotoxicity in animal models. Despite the intensive study of this system, we still do not fully understand how it is regulated, which forms the basis for my research.

Message for Young Students

I hope that young students can maintain a healthy work-life balance as graduate study can be demanding, but it is a great opportunity to work on something you are fascinated with. There will be many obstacles in front of you, but never struggle on your own. Do not be afraid to ask for help and advice from your supervisor and friends, you are not alone. Graduate studies are challenging and demanding in many ways, but never give up and just enjoy!

INTERVIEW 02

Why RIMD

My story started since I was a nine-year-old child who likes to watch Japanese animation, and since that time, I have developed an interest in Japan and Japanese culture.
As I grew up this interest also matured and after I finished my undergraduate degree in medical microbiology and immunology, I decided to do my postgraduate study overseas. I wanted to acquire more knowledge and experience a new world and discover and learn other modern techniques in my field, and I was destined to go for Japan, the place where I have been longing to go since childhood.
I received a Japanese government scholarship (MEXT) and I was honored to be accepted at RIMD which is one of the most famous and sophisticated institutes in the field of medical microbiology. I believed that RIMD would be ideal place where I can learn the modern techniques in the molecular microbiology field and would afford me wonderful research world. All while allowing me to solve the interesting mysteries of the pathogenic microorganisms.

A Day in the Life

The laboratory environment at RIMD is convenient and comfortable, because of the fully supported facility and the unlimited support of my supervisor and lab mates who are very kind and patient, and they do not hesitate to offer help any time.
At RIMD, I spend my lab life enjoying the performance of many types of experiments, improving my skills in conducting scientific presentations, learning how to think critically, solving the problems and overcoming the research hurdles. In addition to the interesting research life in the lab, I also get to enjoy my hobby of speaking Japanese while communicating with lab members or interacting with people anywhere.
I was able to communicate in Japanese before coming to Japan, as I learned how to speak Japanese from watching Japanese animation, and in Sudan I was enjoying meeting and going out with my Japanese friends, and thanks for that now my life in Japan is very convenient as I can communicate easily with people while shopping, traveling, or doing any other activity.

Research Interest

I studied medical laboratory sciences in my undergraduate and specialized in medical microbiology and immunology. After my graduation, I worked as a teaching assistant at University of Medical Sciences and Technology and as a laboratory specialist in the hospital. It was during this period that I developed my interest in molecular microbiology, since these molecular techniques were becoming increasingly common in modern medical laboratory analysis and diagnosis.
I was happy to be accepted as a member of Professor Horiguchi's team in the molecular bacteriology department of RIMD, which aims to understand the pathogenicity and the mechanisms by which pathogenic microorganisms establish infections and cause diseases in different hosts. In our lab we use the *Bordetella* species as a model along with variety of molecular techniques to conduct our research.
My current project includes the identification of the *B. bronchiseptica* genes, which may be involved in establishing adhesion and colonization within the host respiratory tract using molecular methods. Understanding this mechanism of pathogenicity may assist in designing new strategies and therapeutics to facilitate better disease control.

Message for Young Students

Conducting research is not easy; you need to be patient and work hard to reach your goals and achieve your dreams.
You will face many obstacles and mountains through your way, but do not surrender or lose hope. Remember that, any time you fall down, get up, and shake off the dust of past faults, believe in yourself and be confident, and try to learn from your mistakes.
And if you choose RIMD as the place to realize your dreams and satisfy your passion for research, I can say ... (Congratulations for your right choice). I wish you a wonderful journey of exploring the amazing secrets of the microbiological world.

Shymaa Ali Saeed Ali

Department of Molecular Bacteriology
Doctoral course in Graduate School of Frontier Biosciences

BSc:Department of Medical Microbiology, Faculty of Medical Laboratory Sciences, University of Khartoum, Sudan

RIMD STAFF

Staffs

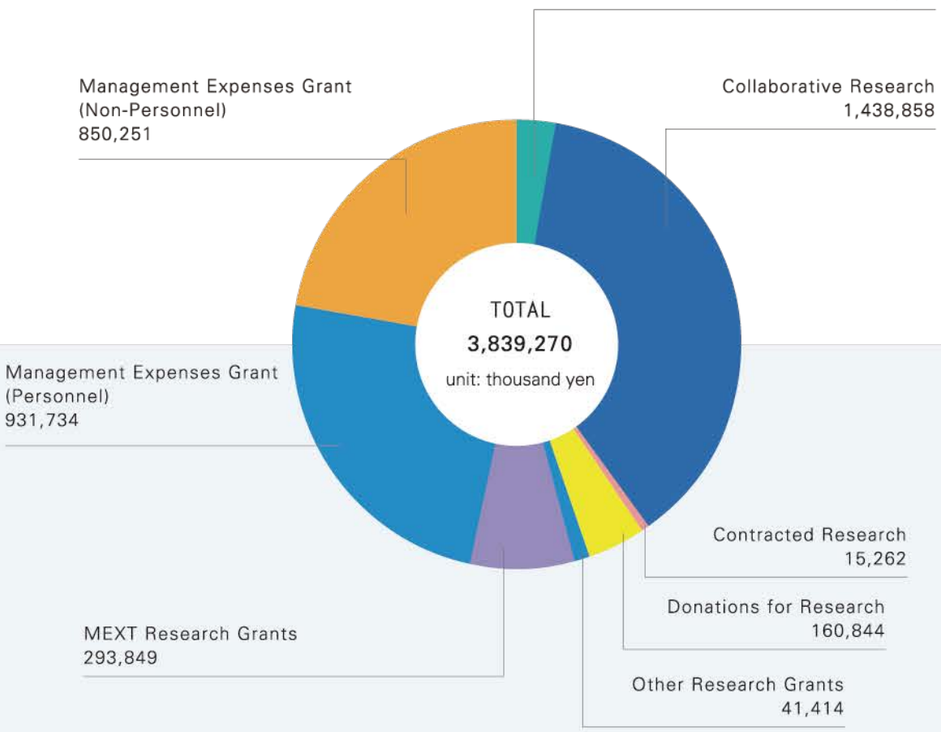
Professor	16
Endowed Chair Professor	2
Associate Professor	16
Endowed Chair Associate Professor	1
Assistant Professor	26
Endowed Chair Assistant Professor	1
SA Professor	3
SA Associate Professor	7
SA Assistant Professor	7
SA Researcher	36
Educational Support Staff	2
Technical Staff	3
SA staff	25
Part-time General and Technical Staff	36
Administrative Staff	25
Total	206

Graduate Students

	①	②	
Graduate school of Medicine	40	8	48
Graduate school of Science	4	17	21
Graduate school of Pharmaceutical Science	6	5	11
Graduate school of Frontier Bioscience	22	-	22

①Doctoral Program
②Master's Program

ACCOUNTS



BUILDING AREA

⑦ Central Laboratory for Biological Hazardous Microbes

⑪ Cutting-edge Research Building for Infectious Diseases(left)
① Main Building
⑩ Integrated Life Science Building(right)

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
④Animal Resource Center A	2	768	1,548
⑤Animal Resource Center A (Old)	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

Osaka University
Suita Campus

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

Train

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

Monorail

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

Bus

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

・From Hankyu Ibaraki-shi Station:
12-minute walk from "Handai Honbu Mae" Bus Stop on buses heading to "Handai Honbu Mae" (via JR Ibaraki Station).

Support RIMD Research

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

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

How your donations are utilized

- **Supporting RIMD researches overseas.**
- **Helping student to study in RIMD (Scholarships etc.)**
- **Helping international students to study in RIMD.**
- **Helping Training Course on Tropical Infectious Diseases for clinical doctors.**
- **Organizing scientific lectures and seminars for non-scientists**
- **Development of the new vaccines and treatments for COVID-19**

[How to donate]

Credit card, Bank transfer

For detail please check the website

https://www.miraikikin.osaka-u.ac.jp/en/

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