

INSTITUTE OF TROPICAL MEDICINE NAGASAKI UNIVERSITY

through Scientific Discovery and its Application Solving the World Health Problem



JULY



2020

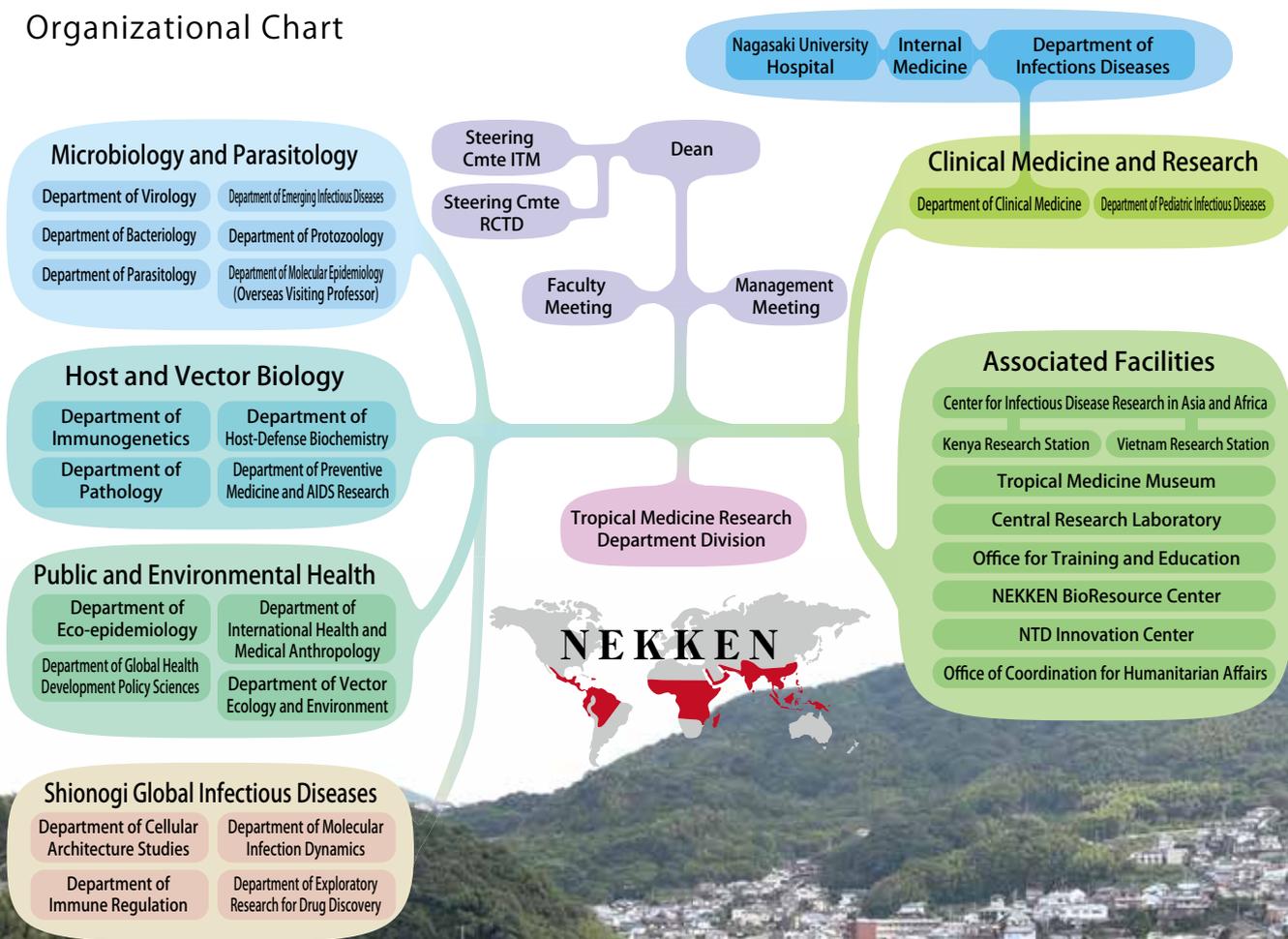
Mission Statement

The tropics, the most ecologically diverse region on the Earth, presents an ongoing complexity of tropical diseases and other health problems. In view of the remarkable advances made in the field of international exchange in recent years, it is imperative that these problems be addressed from a global perspective.

Based on this understanding, the Institute of Tropical Medicine, Nagasaki University, aims to overcome tropical diseases, particularly infectious diseases, and the various health problems associated with them. In cooperation with related institutions, we strive for excellence in the following areas:

1. Spear-head research in tropical medicine and international health
2. Global contributions through disease control and health promotion in the tropics by applying the fruits of our research
3. Cultivation of researchers and specialists in the above fields

Organizational Chart



Steering Committee for the Institute of Tropical Medicine (Committee Member outside the university)
 Hiroyoshi Endo (St.Luke's International University) , Norio Ohmagari (National Center for Global Health and Medicine) ,
 Hitoshi Oshitani (Tohoku University), Shigeyuki Kano (National Center for Global Health and Medicine) ,
 Gakunan Gen (Obihiro University of Agriculture and Veterinary Medicine) , Yasuhiko Suzuki (Hokkaido University) ,
 Takaji Wakita (National Institute of Infectious Diseases) , Tiho Watanabe (National Institute for Environmental Studies)

Towards Eradication of Tropical Infectious Diseases

Institute of Tropical Medicine (NEKKEN), Nagasaki University is a unique governmental institution for research on tropical medicine. The Ministry of Education, Culture, Sports, Science and Technology (MEXT) designated NEKKEN as a "Joint Usage / Research Center on Tropical Disease" in 2009. This recognition underlines the importance of NEKKEN as an open institute whose resources are freely available to the whole research community in Japan. Since 1993, the World Health Organization has designated NEKKEN as a WHO Collaborating Centre for Reference and Research on Tropical Viral Diseases. The current organization of the institute involves five major research fields (21 departments), two facilities, and one clinical unit at University hospital.

Many developing countries are located in the tropics, and are affected by a diverse group of tropical diseases, and emerging infectious diseases. As a consequence the remarkable advances made in the field of international transportation and communication in recent years, the industrialized countries of the temperate zones are also threatened by the same pathogens and it is imperative that they are addressed from a global perspective. Based on this paradigm, NEKKEN aims to overcome tropical and emerging infectious diseases, and the various related health problems in the tropics, in cooperation with related institutions, and to strive for excellence in the following areas:

1. Spear-head research in tropical medicine and global health
2. International contribution through disease control and health promotion in the tropics
3. Cultivation of researchers and specialists in the above fields

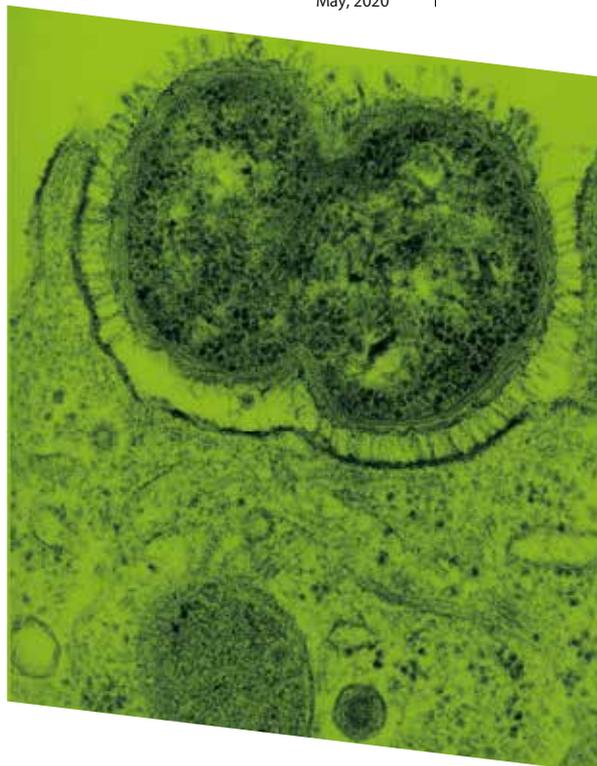
This pamphlet offers a brief, but hopefully intelligible explanation of our organization and its activities. As you will see, our research activities address major tropical diseases such as malaria, schistosomiasis, dengue fever, and yellow fever, and emerging and re-emerging infections such as HIV/AIDS, SARS, ebola and tuberculosis. We conduct basic medical sciences, epidemiology and clinical research for disease prevention and control. We also investigate entomology, ecology and social sciences. NEKKEN is also contributing to the education of students in PhD, and Masters as part of the Graduate School of Biomedical Sciences and the Graduate School of Tropical Medicine and Global Health of Nagasaki University. In addition, NEKKEN provides a three-month training course on tropical medicine. You will also find information about our research facilities in Kenya and Vietnam.

Hopefully you will be able to understand the intention of our research and education and will support us in the future.

Kouichi, Morita
Dean and Professor
NEKKEN
May, 2020

History

- 1942.3 East Asia Institute of Endemics as Nagasaki Medical College affiliate
- 1946.4 Institute of Endemics, N.M.C
- 1949.5 Institute of Endemics, Nagasaki University, under postwar scheme
- 1967.6 Institute of Tropical Medicine, N.U.
- 1967.6 Added the Ward Tropical Internal Medicine, to University Hospital
- 1978.4 Diploma course, Kensyu-katei
- 1983.4 JICA Researcher Group-Course
- 1989.5 Certified as Joint Usage Research Center
- 1993.11 WHO Collaboration Center
- 1995.4 Certified as Center of Excellence, COE
- 1997.4 Tropical Infection Research Center
- 2003.4 COE program 21st Century Global Strategy against Tropical & Emerging Infection
- 2006.4 Tropical Medicine Master's Course
- 2008.4 Museum and Asia / Africa Facilities
- 2008.6 COE program Comprehensive Global Strategy against Tropical & Emerging Infection
- 2009.6 Certified as Tropical-medicine Joint Usage / Research Center
- 2011.4 Two clinical-field departments
- 2012.4 Global Leader Course for Tropical & Emerging Infection Intervention
- 2017.11 75th anniversary ceremony
- 2019.4 Shionogi Global Infectious Diseases Division



Joint Usage / Research Center on Tropical Disease

Our institute is the one and only public sector institute supported by MEXT (Ministry of Education, Culture, Sports, Science and Technology, Japan) that aims to conduct research on tropical diseases, and is identified as the Joint Usage / Research Center on Tropical Disease.

1. The Goal of the Center

Infectious diseases are caused by the collapse of symbiosis with other creatures, which cannot be avoided if we, human beings, live in nature. Although the ultimate aim of this center is to eradicate infectious diseases, it is needed rather to establish reciprocal relationships with other creatures than to eliminate them. Such establishment of reciprocal relationships requires collective knowledge, which can be achieved only by combining a broad aspect of disciplines.

Tropical infectious diseases have been spreading in tropical areas, which is a reflection of the environment and socio-economic situation existing there. It is considered to be a big challenge related to health. Emerging and re-emerging infectious diseases have been spreading globally with tropical areas at the epicenter. Tropical areas are not only the battle field where we, human beings, fight against them, but also the experimental ground where we newly create and develop our knowledge and technology in order to control infectious diseases.

Against the backdrop of past international activities and research facilities for infectious diseases in Asia and Africa, the Joint Usage / Research Center on Tropical Disease, together with researchers from diverse fields,

carries out joint research rooted in the local places where the infectious diseases are prevalent.

2. Outline of the Center's Activities

The Joint Usage / Research Center on Tropical Medicine supports collaborative research, which is either basic or applied research based upon an epidemiological, clinical or public health framework. It also supports research meetings, which promote and facilitate research into infectious diseases through exchanging information or technology where necessary. The Center serves as a bio-resource center to deliver such things as infectious agents, information, collected and stored here.

3. Operational Organization of the Center

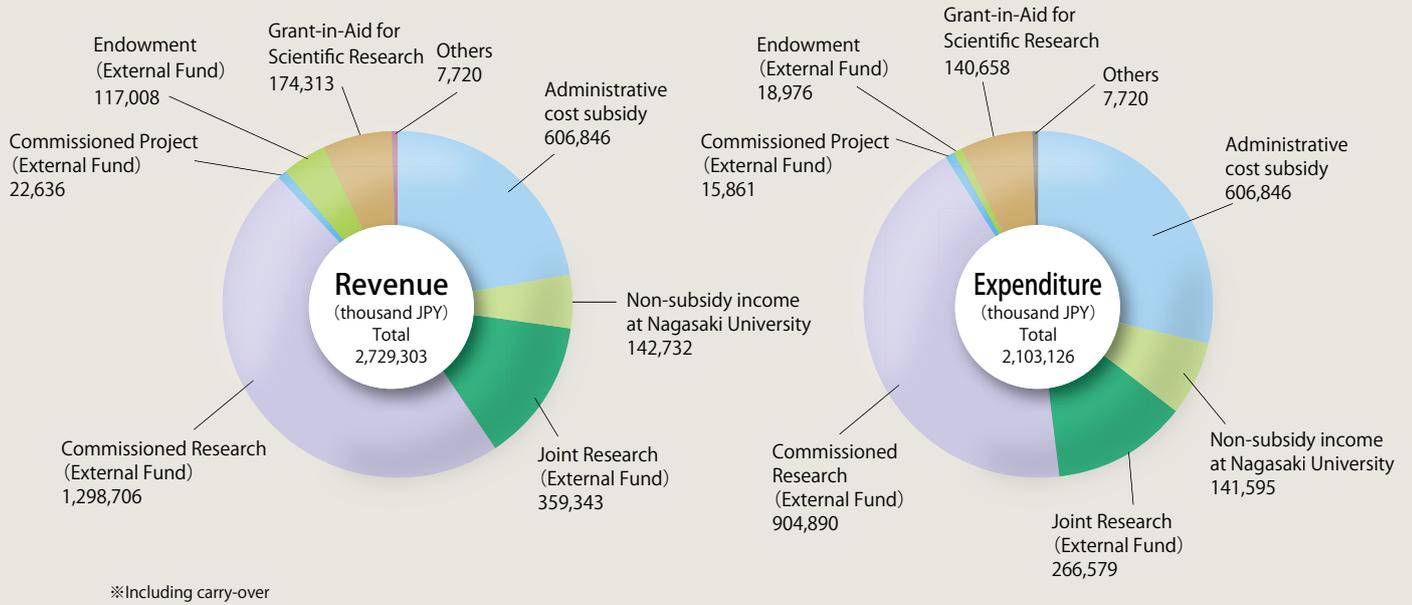
As for administration of this research center, the dean of the Institute of Tropical Medicine established the Steering Committee for the Center, which is composed of 11 members, out of whom more than half should be from outside the university concerned. The Steering Committee is responsible for the adoption of the applications, and monitoring and evaluation of the activities.

In order to support the above mentioned activities a specific administrative office supporting the Center is allocated in the institute and a professor is designated to be a section chief.

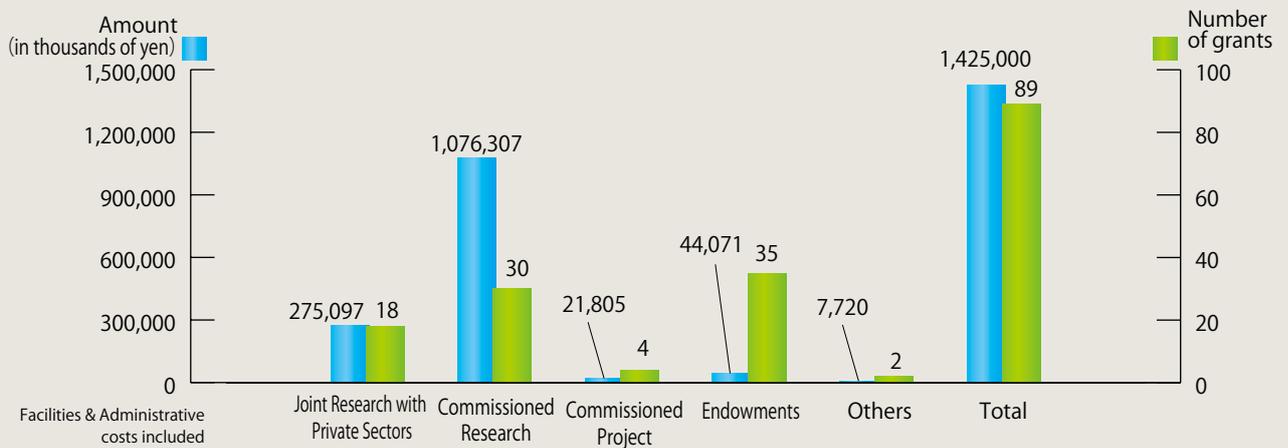


Steering Committee for the Joint Usage / Research Center on Tropical Disease (Committee Member outside the university)
 Manabu Ato (National Institute of Infectious Diseases),
 Shinichiro Kawazu (Obihiro University of Agriculture and Veterinary Medicine), Satoshi Sasaki (The University of Tokyo),
 Yukiko Higa (National Institute of Infectious Diseases), Sohkichi Matsumoto (Niigata University),
 Chizuru Misago (Tsuda University), Takayuki Miyazawa (Kyoto University)

Accounting (FY2019)



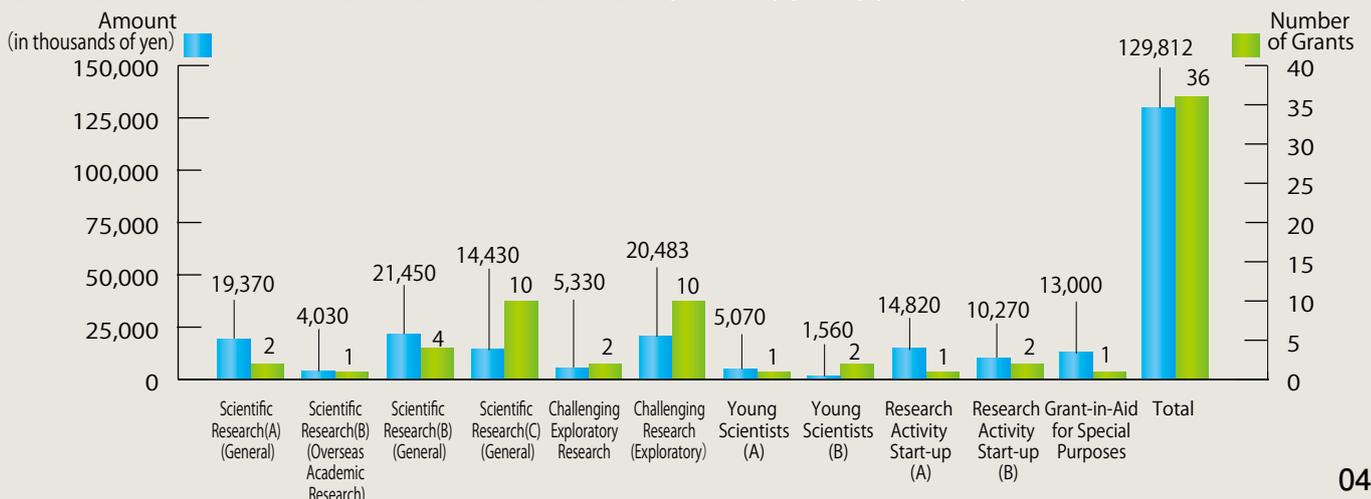
External Fund (FY2019)



Number of Staff (as of May 1, 2020)

Professor	Associate Professor	Senior Assistant Professor	Assistant Professor	Sub total	Others	Total
15	7	1	24	47	101	147

Grants-in-aid for Scientific Research (KAKENHI) (MEXT) (FY2019)



Microbiology and Parasitology Department of Virology



Professor and Head
Kouichi Morita
Professor
Moi Meng Ling
Associate Professor
Shingo Inoue
Assistant Professor
Takeshi Nabeshima
Assistant Professor
Mya Myat Ngwe Tun

This Department has been conducting basic and applied research on arthropod-borne viruses (arboviruses) such as Japanese encephalitis virus (JEV), dengue virus (DENV), Zika virus (ZIKV), Chikungunya virus (CHIKV), severe fever with thrombocytopenia syndrome virus (SFTSV) and COVID-19 virus (SARS-CoV-2)

Molecular epidemiology of arboviruses

We isolate DENV, JEV, CHIKV, ZIKV and SARS-CoV-2 in Asia and African regions and conduct molecular epidemiological analysis to determine international and inter-continental movement of these viruses. We also analyze unique genome sequences that are relevant to pathogenicity.

Research on vaccine development using reverse genetics

We have developed DENV infectious clones and identified viral determinants by modifying various parts of the genes. We are currently developing genetically engineered viruses as candidates for live attenuated DENV vaccines by financial support of GHIT.

Research on the pathogenicity of arboviruses and evaluation of therapeutic compounds using animal



model.

We elucidate the mechanism of pathogenicity and infectivity of arboviruses, such as DENV and SFTSV by using a mouse model.

Development of rapid diagnostic assay for infectious diseases

Various rapid diagnostics are being developed for arboviruses using PCR, LAMP, LC/MS and Immuno-chromatographic technologies for the detection of viral genome, protein and specific antibodies.

Activities as a WHO Collaborating Center

The department is designated as a WHO Collaborating Center for Reference and Research on Tropical Viral Diseases since 1993 and currently our department has been re-designated as a center for Tropical and Emerging Virus Diseases. The center has been collaborating with WHO in training WHO fellows from many developing countries and has deployed experts as WHO short-term consultants. From 2020 March, the laboratory is working as WHO Reference Centre for COVID-19.

1. Le et al. *Emerg Infect Dis* 2020; 2: 26(7).
2. Wijesooriya et al. *Lancet Infect Dis* 2020; 20(2): 168-169.
3. Bastola et al. *Lancet Infect Dis* 2020; 20(3): 279-280.
4. Kyaw et al. *Am J Trop Med Hyg* 2019; 100: 643-646.
5. Yamane et al. *Nat Microbiol* 2019; 4(7): 1096-1104.

Microbiology and Parasitology Department of Bacteriology

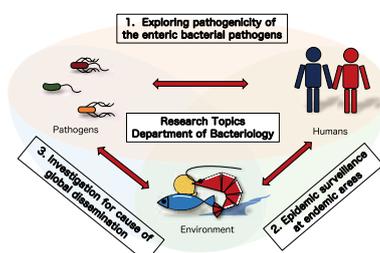


Professor
Toshio Kodama

Our research focuses on the pathogenesis of enteric bacterial pathogens, including *Vibrio parahaemolyticus*, *Vibrio cholerae*, and *Salmonella enterica* spp. The emergence and spread of multidrug-resistant bacteria are big problems these days. It is predicted that drug-resistant bacterial infection will bring about 10 million annual deaths by 2050. We believe that understanding detailed mechanisms of bacterial pathogenicity gives us a clue to the development of effective vaccines and establishment of new treatment strategies without antibiotics. We will promote our study with various approaches, such as global epidemic surveillances, *in vivo* animal infection models, and *in vitro* molecular biological analyses, and make maximum efforts to produce talented researchers who can play on a global stage through study and experience.

● *V. parahaemolyticus* Pathogenesis

We have worked on *V. parahaemolyticus* for decades, and found that one set of Type III Secretion System (T3SS2) is necessary for induction of diarrhea in the patients infected with this pathogen. We have also identified and characterized effector proteins secreted from T3SS2, and revealed regulatory mechanisms of T3SS2-related genes. We recently demonstrated that an exotoxin, thermostable direct hemolysin (TDH), is secreted via T3SS2 in tandem with the Sec machinery, facilitates the distinct virulence traits. However, detailed mechanisms of how this pathogen colonizes the host intestine and induces diarrhea have remained unknown. We therefore try to understand a comprehensive mechanism of *V.*



parahaemolyticus infection by generating a new murine infection model, dissecting the expression mechanism of T3SS2-related genes, determining biological activities of T3SS2 effectors, analyzing the interaction of microbiota, and other multidimensional approaches.

● Endemic Stains of *Vibrio* spp.

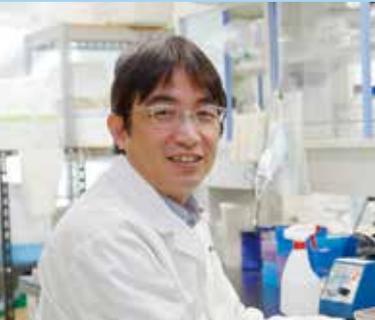
We are planning to isolate *Vibrio* spp. including *V. parahaemolyticus* and *V. cholerae* from patients, seafood and environmental samples in endemic areas to elucidate the genetic characteristics and dynamics of epidemic strains. We will also try to determine the factor(s) that contributes to global dissemination and characterize its role in infection.

● *Salmonella* Pathogenesis

We are interested in *Salmonella* pathogenesis. A big goal in this project is to understand how *S. enterica* spp. cause systemic infection in immunocompetent humans for developing more effective vaccines and therapies without relying on antibiotics. The Type III Secretion System (T3SS) coded on *Salmonella* Pathogenicity Island 2 (SPI-2) is known as an essential virulence factor for establishing systemic infection and resisting the defense system of innate immune cells, such as macrophage and neutrophil, but its exact mechanism to disseminate into systemic sites in the host remains unknown. We have tried to uncover the mechanism, how *S. enterica* spp. cause systemic infection by dissecting the functions of the T3SS and its effector proteins using various approaches, including *in vivo* mouse infection models, *in vitro* biological assays, epidemic surveillance, and *in silico* genetic comparisons among different *S. enterica* serovars (i.e., Typhimurium, Typhi, and Paratyphi A).

1. Kashimoto et al. *BMC Microbiol* 2020; 20(1): 69.
2. Matsuda et al. *Microbiol Immunol* 2020; 64(3): 167-181.
3. Okumura et al. *Mucosal Immunol* 2020; 13(1): 75-85.
4. Matsuda et al. *Nat Microbiol* 2019; 4(5): 781-788.
5. Tandhavanant et al. *mBio* 2018; 9(4): e01366-18.

Microbiology
and Parasitology
Department of Emerging
Infectious Diseases



Professor
Jiro Yasuda
Professor
Asuka Nanbo
Assistant Professor
Haruka Abe
Assistant Professor
Yasuteru Sakurai
Assistant Professor
Rokusuke Yoshikawa

We are working on the basic and applied research to develop the countermeasures against emerging infectious diseases, especially viral hemorrhagic fevers and influenza.

**Research subjects:
Analyses of replication mechanisms of highly pathogenic viruses**

In infected cells, the viruses replicate using various cellular machinery and release a large number of progeny virions. Our interests are to clarify the molecular mechanisms of virus replication in host cells. We are currently analyzing the molecular interactions between viral proteins and cellular factors in infected cells. Especially, we are focusing on highly pathogenic viruses, such as Ebola, Marburg, Lassa and Influenza viruses.

Development of novel antiviral strategies

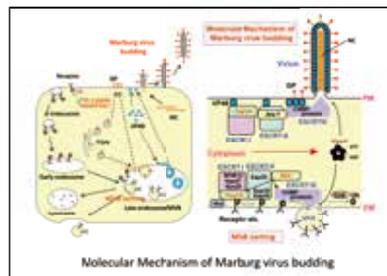
To establish novel antiviral strategies against viral hemorrhagic fevers and influenza, we are identifying the cellular factors which have antiviral activity and analyzing the molecular mechanisms of their antiviral action. We are also doing high-throughput screening of organic and chemical compound libraries for antiviral drug discovery against viral hemorrhagic fevers.

Development of detection methods for highly pathogenic viruses

In case of outbreak of emerging infectious diseases, rapid and accurate diagnoses are essential to control infection and to prevent further transmission. We have developed novel diagnostic assays for emerging viral diseases.

Research studies on viral diseases in Gabon republic

The followings are aims of this project; 1) to investigate prevalence of known and unidentified viral diseases in Gabon through genetical and serological assays, 2) to determine characteristics including genetic information and pathogenicity of viruses which are regarded as public health concern and those newly identified in Gabon, and 3) to develop rapid diagnostic methods for viral diseases of public health concern and those newly identified.



1. Abe et al. *Int J Infect Dis* 2020; 91: 129-136.
2. Abe et al. *J Med Virol* 2020; 92(2): 251-256.
3. Urata et al. *J Gen Virol* 2019; 100(7): 1099-1111.
4. Yoshikawa et al. *J Virol* 2019; 93(10): e02226-18.
5. Pemba et al. *J Virol Methods* 2019; 269: 30-37.

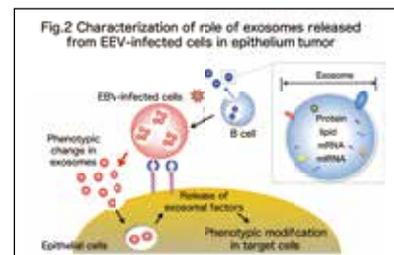
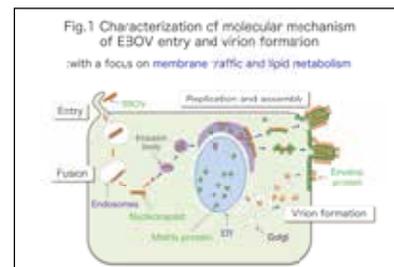
Ebolavirus and Epstein-Barr virus both cause major infectious diseases in humans, such as Ebola virus disease and Epstein-Barr virus-associated malignancies, respectively. The long-term goal of our study is to provide insights into the molecular mechanisms of their pathogenesis, which shall lead to the development of rational therapies and diagnosis for them.

● Characterization of molecular mechanisms of EBOV entry and virus particle formation: toward the development of therapeutics for EBOV disease

Ebolavirus (EBOV), a member of the family *Filoviridae*, is an enveloped, single-stranded, negative-sense RNA virus that causes severe hemorrhagic fever with a high mortality rate, known as EBOV disease (EVD), in humans and nonhuman primates. Currently, no specific therapeutics has been approved for treatment and prevention of EVD. Because of the likelihood of future outbreaks and generation of mutant viruses, the development of a variety of EBOV therapeutics is urgent. Our goal is to elucidate the mechanism underlying virus entry and virion formation process with a focus on host membrane traffic dynamics and viral envelope's constituent phospholipids (Fig.1). We are also developing the therapeutics that specifically target the entry and virion formation process in multiple ways, which should lead to the significant contribution for prevention of EBOV infection in the future.

● Characterization of molecular mechanism of development of EBV-associated epithelium tumors

Epstein-Barr virus (EBV), a ubiquitous human γ -herpesvirus, establishes a persistent latent infection in B lymphocytes and epithelial cells in more than 90% of adults worldwide. Although this virus contributes causally to lymphomas and epithelial malignancies such as Burkitt's lymphoma, gastric carcinoma, and nasopharyngeal carcinoma, the molecular mechanism by which EBV cause these tumors remains fully elucidated. To update the understanding of the mechanisms for development of EBV-associated epithelial tumors, we are elucidating the physiological significance of exosomes, one type of extracellular vesicles, released from EBV-infected cells in tumor development. Moreover, we try to identify host and viral factors that are specifically and abundantly incorporated in exosomes, which shall lead to the development of potential biomarkers for EBV-associated tumors that contribute to the diagnosis of these tumors. An outline of this project is shown in Fig.2.



1. Nanbo. *Microorganism* 2020; 8: 729.
2. Kheir et al. *Cancers* 2019; 11(6): E759.
3. Nanbo et al. *J Infect Dis* 2018; 218(suppl_5): S388-S396.
4. Nanbo et al. *Cancers* 2018; 10(7): E237.
5. Nanbo et al. *PLoS Pathog* 2018; 14(1): e1006848.

Microbiology and Parasitology

Department of Protozoology



Professor
Osamu Kaneko
Assistant Professor
Kazuhide Yahata
Assistant Professor
Takahiro Ishizaki

Malaria is responsible for a huge burden of death and disease in large areas of the tropical and sub-tropical world. Unfortunately, those countries hardest hit by the disease are often amongst the poorest. Despite continuing efforts, there is still no effective vaccine against the disease. In order to design and implement effective disease intervention strategies, we believe that one of the key priorities in malaria research should be the strengthening of our understanding of the basic biology of the parasite. We are currently investigating some

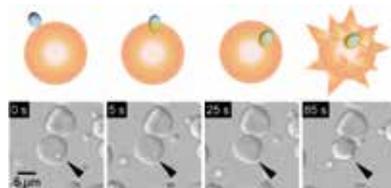


Fig.1 RBC invasion by *P. yoelii*. Merozoite-stage parasite (arrowhead) invades into RBC within 30 seconds (0 - 25 s) and deforms RBC to spike-like shape (85 s).



Fig.2 Colocalization of recombinant PkSBP1 protein (green) and Giemsa-stained 'Sinton and Mulligan' stipplings in monkey erythrocytes infected with PkSBP1-transgenic *P. knowlesi*.

fundamental aspects of the parasite's life cycle, such as the molecular interactions and signaling mechanisms behind red blood cell (RBC) invasion and the phenomenon of cytoadherence of parasite-infected RBCs. We utilize a variety of malaria parasites including human-infecting *Plasmodium falciparum*, the rodent malaria parasite *Plasmodium yoelii*, and *Plasmodium knowlesi* a causative agent of zoonotic human malaria. To expand a platform for basic and clinical malaria research, we are investigating the molecular epidemiology of malaria parasites in endemic countries, the biology of *Plasmodium vivax* hypnozoites, and the establishment of a novel malaria model using ungulate *Plasmodium*. In addition, we are also conducting research about the function and expression mechanism of trans-sialidase and the stage specific adaptation mechanisms of *Trypanosoma cruzi* that cause Chagas disease.

1. Ishizaki et al. *Parasitol Int* 2020; 76: 102056.
2. Peng et al. *mBio* 2020; 11: e02995-19.
3. Thawnashom et al. *PLoS ONE* 2019; 14: e0226884.
4. Chitama et al. *Parasitol Int* 2019; 71: 186-193.
5. Kaewthamasorn et al. *Sci Rep* 2018; 8: 5827.

Microbiology and Parasitology

Department of Parasitology



Professor
Shinjiro Hamano
Assistant Professor
Yoshinori Mitsui
Assistant Professor
Risa Nakamura
Technologist
Megumi Hamasaki

Various kinds of parasites infect humans for long periods of time without killing them, giving rise to tremendous afflictions, social and/or economic loss. We would like to develop deep insight into parasitic diseases and the surrounding factors from various points of view through both field and laboratory studies. Our goal is to contribute to new knowledge and to provide an enthusiastic environment for the training of the future generation of investigators.

We have been researching parasitic diseases in Mbita and Kwale, Kenya, in cooperation with Kenya Medical Research Institute (KEMRI) and Maseno University. In 2017, we started a new project on schistosomiasis with the support from MEXT Grant-in-Aid for Scientific Research (A). We are also trying to develop ideal diagnostic methods for schistosomiasis and leishmaniasis with the



support from Global Health Innovative Technology Fund (GHIT). In the laboratory, we maintain *Schistosoma mansoni*, its intermediate host snail, *Brugia malayi*, *B. pahangi* and *Aedes aegypti*. Since 2017, we have been conducting "DeWorm3" project in Japan which is supported by the Bill & Melinda Gates Foundation as a collaboration with the Natural History Museum, London.

We study host defense mechanisms against *Leishmania spp* and *Trypanosoma cruzi*, and in the process, have elucidated the function of the IL-12 cytokine family such as IL-27/WSX-1 during infection. We have been developing the live attenuated vaccine to leishmaniasis and trypanosomiasis by editing a gene using CRISPR-Cas9 system with the support from GHIT since 2015 and 2019. In addition, we developed animal models of intestinal amoebiasis together with Prof. Houpt at University of Virginia, and now are devoting ourselves to the study on molecular basis of pathogenicity of *E. histolytica* and host defense mechanisms to it.

1. Mohammed et al. *PLoS Negl Trop Dis* 2020; in press.
2. Zhang et al. *Nat Commun* 2020; 11(1): 3461.
3. Sassa et al. *PLoS Negl Trop Dis* 2020; in press.
4. Mousa et al. *Parasitology* 2020; 1-24.
5. Hasegawa et al. *PLoS Negl Trop Dis* 2020; 13(1): 6.

Host and Vector Biology
Department of Immunogenetics



Professor
Kenji Hirayama
 Professor
Katsuyuki Yui
 Lecturer
Mihoko Kikuchi
 Assistant Professor
Taeko Naruse

This department primarily focuses on the fundamental insights of the pathogenic genetic factors of the host and the pathogens of tropical infectious diseases such as Dengue fever, malaria and Chagas disease, through the application of immunology and genetics. With the understanding of the dynamic host-pathogen interactions, we are further concerned with the development of new tools to fight against these diseases including novel therapeutics (drugs) or vaccines.

We strive to build a highly interactive and collaborative network for sustainable research activities, and hence, we have various well-arranged collaborative projects with the following overseas and domestic facilities. 1) Research Institute for Tropical Medicine (RITM), Philippines. 2) UAGRM, Bolivia, 3) IICS University of Asuncion, Paraguay, 4) Pasteur Institute in Ho Chi Minh City, and National Institute of Hygiene and Epidemiology (NIHE), Vietnam, 5) Ahmadu Bello University, Nigeria, 6) Pasteur Paris, France, 7) London School of Hygiene and Tropical Medicine, UK, 8) National Institutes of Health (NIH), USA, 9) Tokyo Medical and Dental University, 10) Toyama University, 11) The National Institute of Advanced Industrial Science and Technology (AIST) 12) IS Global, Spain



Following research projects are going on.

1. Malaria

- 1) NGS analysis of host and malaria genome (KAKENHI)
- 2) Vaccine development (AMED)
- 3) Anti-malarial drug development (AMED, Toyama)

2. Chagas disease

- 1) Early bio-markers identification for chronic Chagas disease, namely, indeterminate, cardiac, and digestive forms in Bolivia (KAKENHI)
- 2) Anti-trypanosomal drug development (Toyama, Nagasaki)

3. Dengue

- 1) Mechanism of cellular immunity on protection against Dengue virus (J-GRID).

1. Tran et al. *J Clin Epidemiol* 2020; 119: 26-35.
2. Mathenge et al. *Parasitol Int* 2020; 74: 101919.
3. Bodi et al. *Malar J* 2020; 19(1): 25-25.
4. Pare et al. *EBio Medicine* 2020; 51: 102584-102584.
5. Vásquez et al. *PLoS Negl Trop Dis* 2019; 13(9): e0007715.

Host and Vector Biology
Department of Host-Defense Biochemistry



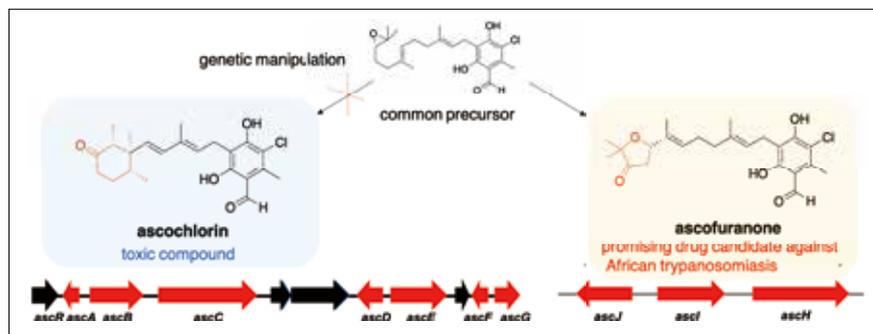
Professor
Kiyoshi Kita

1. Education and research

Aim of our department is to contribute to global health and welfare from basic research. Main target of our research is energy metabolism, which is essential for the survival, continued growth and reproduction of living organisms. From the standpoint of biological adaptation, we have been studying on the molecular mechanism of energy transducing systems

such as mitochondrial and bacterial respiratory chain and drug discovery and development targeting them.

Our research has been focusing on human mitochondria, parasitic nematodes such as *Ascaris suum*, parasitic protozoa (*Plasmodium falciparum*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Cryptosporidium* etc.)



Bio-synthetic pathway of ascofuranone. (from Araki et al., PNAS, 2019)

1. Enkai et al. *Parasitol Int* 2020; 75: 102004.
2. Balogun et al. *FASEB J* 2019; fj201901342R.
3. Wang et al. *Genes* 2019; 10: 471.
4. Araki et al. *Proc Natl Acad Sci U S A* 2019; 116: 8269-8274.
5. Pang et al. *Nat Struct Mol Biol* 2019; 26: 289-296.

Host and Vector Biology
**Department of Pathology
 Nutrition and Infection Unit**



Professor
 Sharon Cox

Department of Pathology, Nutrition and Infection (former Department of Pathology) was established in 2019 by Professor S. Cox (NU School of Tropical Medicine & Global Health (TMGH)) transferring to initiate this new department, separate from the Department of Global Health Development Policy Sciences.

We are interested in how nutrition underpins human health and may mediate interactions between infections and non-communicable diseases such as diabetes. The research aims to provide an evidence base to support nutrition-based interventions to improve health outcomes and includes young children, adolescents, pregnant women and adults in low- and middle-income countries. Much of the current work is focused on Tuberculosis (TB), undernutrition and diabetes in TB patients in the Philippines, with research studies in both inpatient and outpatient populations. We collaborate with investigators from San Lazaro Hospital, Manila, the Nutrition Centre of the Philippines and the National TB programme. Professor Cox is the principle investigator of a large Filipino TB treatment cohort (the St-ATT cohort) (ISRCTN16347615), with active follow-up of patients until 2 years post-treatment. The cohort also includes 3 nested PhD student research projects with collaborators at the London School of Hygiene & Tropical Medicine (LSHTM). Professor Cox is also a co-investigator on a new, UK-funded, multi-country study investigating the role of the pancreas in

long-term effects of malnutrition occurring in child- and adulthood, with data collection in Philippines, India, Tanzania and Zambia, led by Prof Suzanne Filteau at LSHTM.

Other ongoing research includes investigating the determinants of malnutrition of young children within the NHAM birth cohort in Cambodia (National Centre for Global Health, Japan), with a focus on infant feeding, hygiene, infections and the microbiome, collaborating with the Quadram Institute UK.



TB ward at San Lazaro Hospital, Manila

1. Miyazaki et al. *Trans R Soc Trop Med & Hyg* 2020. doi:10.1093/trstmh/traa020(epub ahead of print)
2. White et al. *Sci Rep* 2020; 10(1): 4100
3. Lee et al. *PLoS ONE* 2019; 14(6): e0218193.
4. White et al. *PLoS ONE* 2019; 14(5): e0215968.
5. Shridhar et al. *Curr Dev Nutr* 2019; 3(3): nzy085.

Public and Environmental Health
**Department of
 Eco-epidemiology**



Professor
 Satoshi Kaneko
 Assistant Professor
 Kentaro Kato
 Assistant Professor
 Tomonori Hoshi

Our department is involved in various branches of public health research. With cutting edge IT and biotechnology, we intend: to create more accurate assessment methods in global health, to improve responses to the public health needs on a local level, and to open new directions in health sciences to the future generations. Our activities include the following:

1. Development of Microsphere-Based Simultaneous Multiple Assay System and Surveillance Systems for Multiple Infectious Diseases:

Neglected tropical diseases (NTDs) are spreading across sub-Saharan Africa, but the current assessment on NTDs is still unclear. At the same time, simple and cost-effective methods for monitoring NTDs are needed. To fill in this gap, we are developing a simultaneous multiple antibody detection assay system, utilizing microsphere-based multiplex technology and sampling system for the survey using the satellite images to detect house structures with the University of Tokyo.

2. Civil Registration and Vital Statistics (CRVS) for the Epidemiological Research:

In many developing countries, CRVS systems are still deficient, and this affects the statistical analysis of the population in a given region. For this, the resident registration system for the epidemiological research in a given location called Health and Demographic

Surveillance System (HDSS) was developed. HDSS follows residents, and their dynamics over a long period. We are operating HDSS programs to develop future CRVS system integrating the cloud-based mother and child registration system in Kenya and Laos.

3. Epidemiological studies for healthy growth of children in Africa:

The Kwale district in Kenya is one of the poorest areas with high prevalence of stunted growth. We are conducting epidemiological studies on stunting (shorter than the standard for age). In addition, we will establish a birth cohort regarding pregnancy, birth, and subsequent child development, and also acquire childcare and feeding activities, as well as environmental information, to elucidate the epidemiological basis for investigating factors related to child growth.

4. Research to clarify the molecular bases of parasitic diseases:

Besides field work, basic research especially on schistosomiasis, amoebiasis and leishmaniasis are being conducted in our lab. We are dedicated to apply our achievements from the lab to the field.

5. Research on monkey malaria vectors applying the 3D-printing technology-based original mosquito trap:

We are working in northern Borneo in collaboration with research teams in the UK and University Malaysia Sabah.



1. Hitachi et al. *Int Breastfeed J* 2019; 14: 32.
2. Hoshi et al. *Sci Rep* 2019; 9(1): 11412.
3. Tanaka et al. *Public Health* 2019; 173: 58.
4. Shimazaki et al. *Int J Tuberc Lung Dis* 2018; 22(1): 65-72.
5. Sato et al. *Int J Environ Res Public Health* 2019; 16(16): E2954.

Public and Environmental Health

Department of International Health and Medical Anthropology



Professor
Taro Yamamoto
Assistant Professor
Hiromu Ito

Department of International Health and Medical Anthropology has started its activities since 2008.

Our research was composed of four units; 1) research on infectious diseases in ecosystem, 2) research on the environment health, 3) research on biological evolution of microorganisms from the adaptation or fitness viewpoint and 4) research on the epidemiology from the historical viewpoint. The umbrella concept linking above four research units is to reconstruct infectious diseases "temporally" and "spatially" alike. Infection is the biological phenomenon as an interaction between hosts and microorganisms. In other words, host behavior, social structure as well as culture per se affect microorganisms in fitness and adaptation whereas microorganism has



impact on its hosts. Based on that perception, our department aims to get more detailed understanding and insight on infectious diseases. We would like to pursue the ways of analysis by various approaches such as molecular-evolutional technique, molecular epidemiology, detection of trace DNA, genomics based on bioinformatics, mathematical model, and computer science.

Another pillar of our department is a social responsibility. Now that even profit oriented organizations are required to have its corporate social responsibility, no need to say for academia or university. Out of the name of our department, it must be nothing but contribution to international health or people's health in resource-limited settings. What we think of important is to make solidarity in order to contribute to sustainable development. It is our department's goal.

1. Ito et al. *Sci Rep* 2019; 9: 17408.
2. Tu et al. *BMJ Open* 2019; 9(11): e027659.
3. Ito et al. *PLoS ONE* 2019; 14(8): e0221520.
4. Tsai et al. *J Microbiol Methods* 2019; 164: 105671.
5. Ito et al. *Appl Math Comput* 2019; 348: 363-370.

Public and Environmental Health

Department of Vector Ecology and Environment



Professor
Noboru Minakawa
Associate Professor
Hitoshi Kawada
Assistant Professor
Toshihiko Sunahara
Assistant Professor
Kyoko Futami

Our research interests include anything from ecology to molecular biology of medically important arthropods, particularly mosquitoes that transmit pathogens such as malaria parasites and dengue virus in Africa and Southeast Asia. We are also interested in their relationships with environmental variables and development of environmentally friendly vector control tools.

For dengue virus vectors, we revealed the geographical distributions of two subspecies of *Aedes aegypti* in East and South African regions. Our study also found that the genetic structures of *Ae. aegypti* populations in the endemic areas of Africa are similar to those of

Southeastern populations. The results suggest that the African mosquito populations were introduced from the overseas. To test the hypothesis further, we are currently conducting various studies, including a study on virus susceptibility.

For reducing malaria risk, we are evaluating the effectiveness of new insecticides and insecticide treated mosquito nets (ITNs) in Kenya and Malawi. We are also developing a malaria early warning system in Africa.



1. Kawada et al. *Jpn J Infect Dis* 2020; 73(2): 124-131.
2. Futami et al. *J Med Entomol* 2019. doi:10.1093/jme/tjz233.
3. Yamamoto et al. *Biosens Bioelectron* 2019; 132: 375-381.
4. Kim et al. *Sci Rep* 2019; 9(1). doi:10.1038/s41598-019-53838-3.
5. Sunahara. *Jpn J Infect Dis* 2019; 72(6): 368-373.

Public and Environmental Health

Department of International Health Development and Policy



Professor
Hirotsugu Aiga
Professor
Yasuhiko Kamiya
Professor
Kazuhiko Moji

Department of International Health Development and Policy (former Department of Social Environment) was re-established in 2018 by inviting three concurrent professors from the School of Tropical Medicine and Global Health (TMGH). The three professors have expertise of health system strengthening (H. Aiga), child health and emergency assistance (Y. Kamiya), and human ecology and ecohealth (K. Moji). The department promotes policy researches in various global health fields for making critical evaluation and constructive proposal for health policy.

Health System Strengthening

In the absence of appropriately functioning systems for health service delivery, new medical technologies and drugs that are clinically effective would end up not reaching the populations in need. Key elements of health systems (e.g. health workforce, health information and health financing) particularly in the context of LMICs are one of my research topics. Needless to say, while recognizing the importance of optimization and adaptation of global standards for health systems to local settings, their critical verification and examination in view of field realities are equally important.



An experienced nurse managing a rural health center in Brundi

1. Aiga. *Lancet* 2020; 395(10217): 27.
2. Aiga et al. *BMC Public Health* 2019; 19(1): 773.
3. Aiga et al. *Glob Health Action* 2016; 9(2): 29924.
4. Aiga et al. *BMC Public Health* 2016; 16: 129.
5. Aiga. *BMJ* 2015; 351: H4990.

Implementation Science in Health and Disability

My support and study is focused on redressing health disparity in low- and middle-income countries. Notwithstanding global evidence-based aid and national policy, health disparity has been widening with know-do gap and mismatch (coexistence of excess and deficiency) in health service delivery due to organizational path dependency, lack of coordination, vertical silo of programs and aid fragmentation. Just attributing health disparity to lack of access to, and low supply of health care can mislead and delay its fundamental problems. Through Implementation Science applying to international cooperation for maternal and child health, support for disabled children and non-communicable diseases, and emergency humanitarian assistance, my assistance and research facilitate local staff and people identify bottlenecks and barrier to strengthen health systems and governance based on bottom-up problem-solving.



Training for Community Health Workers in Honduras

1. Akiyama et al. *Health Promot Int* 2020; daaa005.
2. Hitachi et al. *Int Breastfeed J* 2019; 14: 32.
3. Kodaira et al. *J Int Health* 2019; 34(1): 19-25.
4. Tsukakoshi et al. *Virology* 2015; 12: 36.
5. Sasaki et al. *J Trop Pediatr* 2015; 61(1): 14-19.

Health Policy based on Human Ecology

Social determinants of health disparities have been revealed through studies of social epidemiology since the late 20th Century. Health impacts of global climate change as well as global (and local) environmental changes have been revealed almost

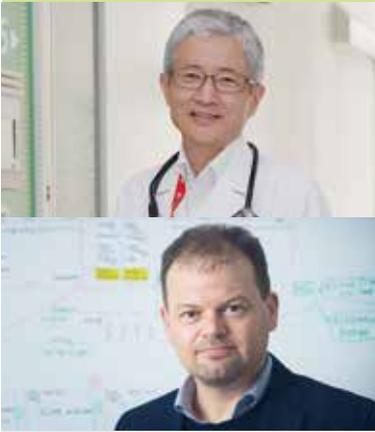


A research field in Laos

simultaneously. To integrate all the factors related to our health, human ecological system thinking, or "ecohealth" thinking is indispensable. For global health (or international health development) policy, not only improvement of medical services but also health promotion and disease prevention by means of better hygiene and safer and healthier lifestyle and non-medical care and social supports should be collectively implemented. Health policy is beyond the narrow medical policy. This department will promote researches on evaluation of health policy on population health for better policy proposal.

1. Sato et al. *Int J Environ Res Public Health* 2019; 16: pii:E2954.
2. Hoshi et al. *Sci Rep* 2019; 9(1): 11412.
3. Pongvongsa et al. *Trop Med Health* 2018; 46: 33.
4. Sato et al. *PLoS Negl Trop Dis* 2018; 12(2).
5. Hashizume et al. *Acta Trop* 2017; 169: 1-7.

Clinical Medicine
and Research
**Department of
Clinical Medicine**



Professor Koya Ariyoshi
Professor Chris Smith
Associate Professor Konosuke Morimoto
Associate Professor Yoshinao Kubo
Assistant Professor Eiichiro Sando
Assistant Professor Momoko Yamauchi

This is the only clinical department in NEKKEN clinical in Nagasaki University Hospital. We conduct a wide range of multi-disciplinary studies our strength of clinical epidemiology to laboratory-based microbiology and immunology both in- and outside Japan. Our main research interests are respiratory infectious diseases, tropical infectious diseases, tuberculosis (TB) and HIV/AIDS. Specific research topics are as described below:

1. Respiratory Infections Diseases

We apply our in-house multiplex-PCR assays to identify 19 different viral and bacterial respiratory pathogens and a novel nano-fluidic real-time PCR-based assay to determine 50 pneumococcus serotypes for a multi-center adult pneumonia survey all over Japan and childhood acute respiratory infection study in central Vietnam. We published several papers demonstrating vaccine efficacy against pneumococcal pneumonia and influenza. Since 2009, we have run a birth cohort study of about 2,000 pairs of mothers and new-born babies, which facilitates studies of host-gene factors associating the severity of pediatric infectious diseases.



Bed-side clinical training course in San Lazaro Hospital

2. Tuberculosis

For better-diagnosis of latent MTB infection and tuberculosis, we are analyzing cellular immune responses to various TB antigens using an intra-cellular cytokine staining assay to evaluate a range of cytokines profile in various stages of TB infection and their contact cases. Our goal is to clarify TB-specific cellular immune responses characteristic to a different clinical stage of TB infection. We also investigated pathogens causing bacterial pneumonia and its impact on the survival prognosis of TB patients admitted to the National Infectious Diseases Hospital (San Lazaro Hospital) in the Philippines.

3. Fever management in the tropics

We are conducting undiagnosed febrile illness study in the Department of Infectious Diseases, Bac Mai Hospital, Hanoi, Vietnam and the National Infectious Disease Hospital (San Lazaro Hospital), the Philippines, by applying diagnostic tests for leptospirosis and various ricketthial diseases. We also coordinate a bed-side clinical training course in tropical medicine.

4. HIV/AIDS Studies

In collaboration with National Institute of Health, Thailand, Bac Mai Hospital, Vietnam, Philippine General Hospital, and Nagoya Medical Center, we have investigated the pattern of opportunistic infections among HIV/AIDS patients and disclosed different clinical pictures in different geographical settings.

1. Saito et al. *Clin Infect Dis* 2018; 67: 897-904.
2. Sando et al. *Emerg Infect Dis* 2018; 24: 1633-1641.
3. Katoh et al. *PLoS Negl Trop Dis* 2019; 13: e0007928.
4. Yamashita et al. *Front Immunol* 2019; 10: Article2807.
5. Saito et al. *Clin Infect Dis* 2020; Marc11.

Clinical Medicine and
Research
**Department of Pediatric
Infectious Diseases**



Professor Lay Myint Yoshida
Associate Professor Michiko Toizumi
Assistant Professor Mohammad Shah
Assistant Professor Lina Madaniyazi

Clinical Epidemiological Studies on Pediatric Infectious Diseases

The Department of Pediatric Infectious Diseases conducts research on a wide range of infectious diseases with special attention on severe pediatric infectious diseases including pneumonia, diarrhea, and dengue which are the major causes of under 5 mortality. We also investigate congenital infections and its impact on child development. We have setup a field research laboratory and a population cohort study site in Nha Trang, Vietnam. Environmental epidemiology is another area of our interest, focusing on the health impacts of atmospheric environmental changes including climate variability, global climate change and air pollution.

The current research topics,

1. Cohort studies on Pediatric Infectious Diseases in Vietnam: We receive funding from the Japan Initiative for Global Research Network on Infectious Diseases (JGRID), Japan Agency for Medical Research and Development (AMED) to conduct a large population based cohort study on Pediatric Infectious Diseases in Nha Trang, central Vietnam since 2006.

2. Pediatric ARI surveillance: A population based hospitalized Pediatric acute respiratory infection (ARI) surveillance at Khanh Hoa General Hospital, Nha Trang, Vietnam was established to determine incidence, etiology and risk factors for pediatric ARI/pneumonia since 2007. We also investigate the emergence of new viruses and its molecular and clinical importance. In addition, we also investigate the impact or potential of various vaccine introduction on pneumonia and dengue in a population level.

3. Birth cohort study: We have conducted a birth cohort study on 2000 new born babies in Nha Trang, Vietnam since 2009. This study is to study congenital infection and host genetic factors on physical-neurological development of the child and development of severe pediatric infectious diseases. We also set up a new birth cohort study in 2017-2018 to investigate congenital infection including

rubella, cytomegalo, and zika virus and the effect on the child development.

4. Pneumococcal conjugate vaccine (PCV) reduced dosing trial: We received a multimillion dollar grant from Bill and Melinda Gates Foundation to conduct a PCV reduce dosing trial in Vietnam. We believe that the study outcome will change global PCV vaccination strategy to improve the availability of PCV and other vaccines in developing countries.

5. Dengue intra-family transmission in the community: In collaboration with London School of Hygiene and Tropical Medicine, we are conducting a dengue intra-family transmission study in the community in Nha Trang.

6. Environmental epidemiology: We are conducting several studies on health impact of climate change and air pollution on the local and global scale.



PCV vaccination field work in Nha Trang

1. Madaniyazi et al. *Int J Biometeorol* 2020; 64: 367-375.
2. Yoshihara et al. *Infect Genet Evol* 2020; 81: 104264.
3. Wang et al. *Lancet Glob Health* 2020; 8(4): e497-e510.
4. Kitamura et al. *Emerg Infect Dis* 2020; 26(3): 596-600.
5. Toizumi et al. *Sci Rep* 2019; 9(1): 17105.

Shionogi Global
Infectious Diseases

Alliance Coordinator



Professor
Tsuyoshi Kihara

Nagasaki University has entered into a comprehensive cooperation agreement with Shionogi & Co., Ltd. (Head Office: Osaka, Japan) in the field of infectious diseases focused on malaria on February 28, 2019. Through this agreement, Nagasaki University and Shionogi intended to establish Shionogi Global Infectious Disease Division (SHINE) as a collaborative research division at Institute of Tropical Medicine. The aim of the establishment is to accelerate and facilitate the drug discovery research for malaria. Over the next five years, this division will concentrate on studies to understand the life cycle of malaria parasites and the host defense mechanism, which are essential for the diagnosis and treatment of malaria. And final goals are to create an innovate novel drug and vaccine based on the findings from the studies.

Malaria is one of the top 3 infectious diseases worldwide along with AIDS and tuberculosis, and mainly occurs in epidemics in tropical regions and subtropical regions. The efficacy of existing preventive vaccine is insufficient and also a number of parasites have been developing resistance to existing medicines. Therefore, malaria has been a serious threat to human globally.

Our division consists 4 departments, Cellular Architecture Studies, Molecular Infection Dynamics, Immune regulation and Exploratory Research for Drug Discovery. Through the collaboration, Nagasaki University and Shionogi will become a key part of the new open innovation based on the industry-academia

collaboration both domestic and overseas, and will establish a platform aiming at eradication of malaria. We will strive to contribute to the health of people around the world through ongoing provision of the best preventive and therapeutics of malaria.



Shionogi Press Release, Feb28, 2019, Shionogi enters into Comprehensive Cooperation Agreement in the Field of Infectious Disease Focused on Malaria with Nagasaki University

Shionogi Global
Infectious Diseases

Department of Cellular
Architecture Studies



Professor
Fuyuki Tokumasu
Assistant Professor
Shinya Miyazaki

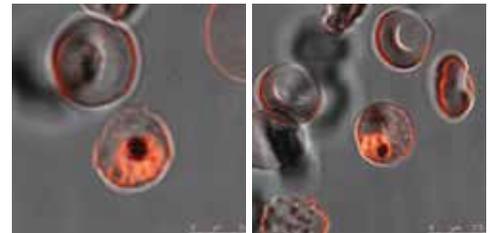
1. Shionogi Global Infectious Diseases Division

Shionogi Global Infectious Diseases Division was established in April 2019, through the collaboration agreement between Shionogi & Co., LTD. and Nagasaki University to tackle malaria. Four laboratories, Departments of Cellular Architecture Studies, Molecular Infection Dynamics, Immune Regulation, and Exploratory Research for Drug Discovery. We share same laboratory space and team up for our mission to find new drug and vaccine candidates by taking advantages of expertise from each department. This is the unique but powerful collaboration that expands our scientific potential and flexibility.

2. Research Activity

Blood stage of malaria parasite invades human erythrocytes and proliferates by creating its own cellular environment. This process includes formations of complex membrane structures inside erythrocyte cytoplasm and transportations of parasite proteins to erythrocyte membrane. Studying this host cell modifications is essential in Plasmodium falciparum research, that often induces severe forms of malaria. We believe that unveiling the molecular mechanisms of structural and chemical balance of parasitized erythrocytes allows us to find important information to

discover a new drug target. We search molecular factors that are involved in 'intelligent interior design' by parasites, and aim to find new antimalarial drug targets and compounds which prevents transition to server malaria. Our research has been merging advantages of classical biochemistry/cellular biology and biophysical approaches. High-resolution imaging, lipidomics, protein chemistry, high-throughput screening for inhibitor compounds have been actively used to achieve our goal. We share our data and collaborate with other three laboratories for advanced experiments for fortifying our scientific competence.



感染細胞内に形成される複雑な膜構造。
感染後まもなく赤血球細胞に大小様々な膜形成が起り始める。

1. Tanaka et al. *Biol Open* 2019; 8: bio042259.
2. Balogun et al. *Biochim Biophys Acta Gen Subj* 2017; 1861(1 Pt A): 2830-2842.
3. Shindou et al. *J Biol Chem* 2017; 292: 12054-12064.
4. Tokumasu et al. *Biol Open* 2014; 3: 529-541.
5. Tokumasu et al. *Exp Parasitol* 2012; 131: 245-251.

Shionogi Global
Infectious Diseases
**Department of Molecular
Infection Dynamics**



Associate Professor
Daniel Ken Inaoka
Assistant Professor
Takaya Sakura

The Department of Molecular Infection Dynamics, in cooperation with Department of Exploratory Research for Drug Discovery aim to identify drug target molecules and to establish screening systems in order to find lead compounds with potential use for treatment, prophylaxis and transmission blocking against malaria.

This Department conduct research on microaerophilic metabolism conserved in several pathogens such as parasites (protozoa and helminth) and bacteria, in order to understand the molecular mechanism of parasitism phenomena.

We utilize multidisciplinary approaches, consisted by biochemistry, molecular biology, biophysics, structural biology and chemical biology, to conduct our basic and applied research.

Our target infectious diseases include protozoan parasites such as *Plasmodium* spp., *Theileria* spp., *Trypanosoma cruzi*, *T. brucei* and *Leishmania* spp.; helminthes such as *Ascaris suum*, *Anisakis* spp., *Haemonchus contortus* and *Fasciola* spp., and bacterial pathogens such as *Mycobacterium* spp. and *Helicobacter pylori*.

We also conduct research on cancer. Intestinal parasites have evolved sophisticated machinery to adapt and survive in hypoxic and nutrient deprived environment (microenvironment). Certain type of cancer cells also possess similar machinery to survive under tumor microenvironment.

Our activities are supported by research grants acquired from KAKENHI (MEXT), AMED, GHIT and Private Companies.

1. Young et al. *BBA-Bioenergetics* 2020; 1861(10): 148247
2. Uno et al. *J Biol Chem* 2020; 295(8): 2449-2463.
3. Enkai et al. *Parasitol Int* 2020; 75: 102004.
4. Balogun et al. *FASEB J* 2019; 33(11): 13002-13013.
5. Araki et al. *Proc Natl Acad Sci U S A* 2019; 116(17): 8269-8274.

Shionogi Global
Infectious Diseases
**Department of
Immune Regulation**



Associate Professor
Shusaku Mizukami

Our scope is the analysis of the human immune response against malaria, especially relate to malaria vaccine development.

The life cycle in human body of the protozoan parasite *Plasmodium*, responsible of malaria, is divided into two stages; erythrocytic and liver- stage. Even with argent appearance of drug resistant strain, there are many current antimalarial drugs available for the erythrocytic stage. On the other hand, for the liver-stage, there are few drugs available with undesirable side effects, thus vaccine and drug development are still an urgent issue for this stage.

Cellular immunity including cytotoxic T lymphocytes (CTL) is considered essential for protection against liver stage malaria. But many vaccine development aim to induce neutralizing antibody, the main effector of humoral immunity, and cellular immunity has not been considered enough.

Therefore, we focus on the liver stage malaria as the target for our cellular immunity based vaccine development. Our plan is to examine and optimize: (a)vaccine antigen which lead the protection by cellular immunity, (b)the antigen delivery system, (c)the adjuvant and route of administration to enhance immune response.

We started our study with mouse malaria model, we aim to apply our research finding for human malaria especially for *Plasmodium falciparum*. We hope our study will contribute to developing better malarial vaccine.

1. Phuong et al. *Ann Clin Microbiol Antimicrobe* 2019; 18(1): 10.
2. Manh et al. *J Gen Viol* 2018; 99(9): 1239-1247.
3. Tani et al. *J Med Chem* 2018; 61(14): 6399.
4. Inokuchi et al. *Arch Viol* 2018; 163(9): 2337-2347.
5. Mosaddeque et al. *Antimicrob Agents Chemother* 2018; 62(5): e02424-17.

Shionogi Global Infectious Diseases
Department of Exploratory Research for Drug Discovery



Visiting Associate Professor
Teruhisa Kato
(Director, Head of Infectious Diseases
3 Group, SHIONOGI & CO., LTD.)

Malaria is one of the three largest infectious diseases in the world, which aligns with HIV and tuberculosis. More than 200 million people are infected with malaria and more than 400,000 people died annually. There has been still no effective vaccine, and resistant malaria to existing therapeutic drugs have been reported, and the development of new drugs is urgently necessary.

In this department, a Shionogi's researcher is in charge of principal investigator, and together with the three departments in SHINE division. We will take on the role of hubs that connect research assets such as know-how and global network of Nagasaki University, and screening drug discovery utilizing the small molecule SAR (structure-activity relationship) engine, which is the strengths of Shionogi, to promote the discovery research of new therapeutic drugs by taking advantage of each strengths. Especially, the purpose is to create a therapeutic drug with strong antimalarial activity and high safety with the department of Molecular Infection Dynamics.

Research activities are as follows:

- Promotion of drug discovery research on screening-based drug discovery
- Implementation of Hit to Lead Structure-Activity Relationship (SAR), and creating lead scaffolds
- Optimization of drug metabolism, safety, and physical parameters of candidate compounds within Shionogi

■ Conducting target discovery and basic research for antimalarial drugs

1. Ryckmans et al. *Bioorg Med Chem Lett* 2011; 21: 4857-4859.
2. Mori et al. *J Pharmacol Exp Ther* 2009; 328: 671-679.

Nagasaki University Institute of Tropical Medicine and Kenya Medical Research Institute (NUITM-KEMRI) Project was launched by signing the Memorandum of Understanding between the President of NUITM, and the Director of KEMRI in 2005. The objective of the project was to enhance research and to develop capacity building in the tropical medicine at the field level. In January 2006, Kenya Research Station was established to manage the project. Biosafety Level 2 and 3 laboratories, and insectary for mosquitos were installed in the station. Research field sites were also established in Mbita near the Lake Victoria, and in Kwale on the coast side of Kenya. Health and Demographic Surveillance System (HDSS) has registered the population of about 120,000 people in the field, as well as vital events like birth, death and migration in two research areas. Additionally, Mosquito Surveillance System (MSS) has been functional for research on malarial mosquitos in Mbita.

1. Research activities:

Basic research teams are organized according to the external research grants or funds. Until now, the SATREPS Project for rapid diagnostics, and the establishment of an alert system for the outbreak of Yellow Fever and Rift Valley Fever were achieved and completed in 2017. AMED-funded project for

serological surveillance on neglected tropical diseases (NTDs) is successfully completed in 2020. We will start research activities toward the formation of IoT academic centers that contribute to the improvement and improvement of global health as an Asia-Africa Science Platforms of Core-to-Core Program supported by the JSPS. There are 13 research activities conducted at Kenya Research Station funded by the JSPS (KAKEN). In addition, our researches are supported by the pharmaceutical companies and the funding agencies such as the Grand Challenge Canada that supports the development of mother and child registration system.

2. Education and training activities:

The station is accepting Master's and PhD students from the Graduate School of Tropical Medicine and Global Health, and the Graduate School of Biomedical Sciences at Nagasaki University. The station is also providing research opportunities for young researchers, and students from Kenyan institutions.

3. Social contribution activities:

We began a JICA Grass-root project focusing on Jigger control in Mbita since 2019, as means for the feedback to the communities.



1. Takeuchi et al. *PLoS Negl Trop Dis* 2019; 13(8): e0007572.
2. Shah et al. *Am J Trop Med Hyg* 2019; 101: 290-293.
3. Shah et al. *Am J Trop Med Hyg* 2019; 100: 688-690.
4. Wandera et al. *Infect Genet Evol* 2018; 68: 231-248.
5. Shah et al. *Trop Med Health* 2018; 46: 30.

Associated Facility
Center for Infectious Disease Research in Asia and Africa

Vietnam Research Station



Chief Representative, Professor
Futoshi Hasebe

Since 2015, the Japan Initiative for Global Research Network on Infectious Disease (J-GRID) project has been taken over to the newly established Japan Agency for Medical Research and Development (AMED) and J-GRID project, this is the final year of the 3rd phase. The 4 main research subjects are dengue fever, infectious diarrhea, influenza, and drug-resistant bacteria, and also severe childhood pneumonia, HIV/AIDS and tuberculosis are included to study to contribute to prevention of infectious diseases collaboration with National Center for Global Health and Medicine, Research Institute of Tuberculosis, Tottori University, Kyoto Sangyo University, and the Kitasato Institute. Furthermore, every year an open lecture on infectious diseases has been held for Japanese residents in Vietnam as outreach activity. In the year 2019, the 12th open lecture was held. Dr Makiko Iijima (WHO Vietnam Country Office) was invited and gave lecture for child illness and vaccination in Vietnam. The Vietnam Research Station in the National Institute of Hygiene and Epidemiology (NIHE) in Hanoi is currently manned by 4 staffs from NU, and the Nha Trang sub-station by a permanent staff of 2 people, in addition to which 6 staff from NU and a further 25 researchers from other research institutions participate in the activities of the Station and conduct research. The Vietnam Research Station has been conducting educational

support as an early exposure facility in the Program for Nurturing Global Leaders in Tropical and Emerging Communicable Diseases that was launched in 2015. Furthermore, the Station is also utilized as an on-the-job-training facility for other researchers not just from NU. In 2017 the Station was visited by 1 undergraduate university students, 2 graduate students, 4 high school students and 1 administrative staff from NU, through which a wide diversity of human resource fostering activities were conducted.

From April in 2020, a new project "Emerging and Re-emerging Infectious Diseases Research Promotion Project in Vietnam" will be started in Vietnam.



A lecture for high school students as Super Global High School's program.



NIHE-NU scientific symposium at Nagasaki University, 2018.

1. Ngwe Tun et al. *Am J Trop Med Hyg* 2020; 102(6): 1217-1225.
2. Wijesooriya et al. *Lancet Infect Dis* 2020; 20(2): 168-169.
3. Hoa-Tran et al. *Infect Genet Evol* 2020; 80: 10419
4. Bui et al. *Jpn J Infect Dis* 2019; 73: 153-153.
5. Hoa-Tran et al. *Infect Genet Evol* 2019; 73: 1-6.

Associated Facility Tropical Medicine Museum



Professor
Junko Okumura
Technologist
Kazuo Araki

The Museum of Tropical Medicine has functions as a resource center on Tropical Medicine. There are sections providing information on tropical diseases, parasites, bacteria, virus, insects (vectors), specimen of dangerous animals, audio-visual materials and historically valuable documents on tropical medicine. The audio-visual section demonstrates interesting scientific movies with 80-inch screen. We have newly established a booth to identify mosquitoes by observation to arouse interest and understanding on tropical infectious diseases for wider age group.

Main activities of the museum in 2019 are categorised in the following three.

● **MUSEUM MANAGEMENT & OPERATION:** The museum provides information on tropical infectious diseases by using approximately 100 panels, microscopic images, movies, specimens, educational models of BSL-4, and PPE (Personal Protective Equipment) for BSL-4.

Since 2018 we organise and operate NEKKEN Summer School targeting young audience such as junior high school and high school students. In addition, we started to exhibit PPE for BSL-3, mosquito net, mosquito mascot (NEKKEN original) and newly established a booth to identify mosquitoes by observation to arouse interest and understanding on tropical infectious diseases for wider age group.



Although main visitors are Japanese, quite a few people visit from overseas. For these foreigners English translated panels are installed in i-Pads and lend them when it is requested. In 2019, we added Chinese (mandarin) translation in the i-Pads.

We collaborate with the event, "BOON-KA-SAI," which was held at National Museum of Emerging Science and Innovation (Tokyo, June 29 – 30 in 2019). In addition to lending it our museum contents, we dispatched a staff to explain on mosquito ecology there. There were more than 3000 attendees.

● **IT (INFORMATION TECHNOLOGY) INFRASTRUCTURE MAINTENANCE:** Network tools and servers are updated with technological innovation and maintaining its security. It provides safe and secure IT environment to researchers, students and staff members who work at NEKKEN.

With IT innovations, the requests from the NEKKEN members are getting wide variety ones. To respond to them we obtain new software and devices as much as possible.

In 2019, we renovated the NEKKEN homepage. Since then we are maintaining the system as well as renewing the contents.

● **RESEARCH:** Prof. Okumura conducts field research in Lao PDR and Republic of Guinea. She collects epidemiological data on infectious diseases, health seeking behavior, nutrition etc. in order to identify factors affect child health. Also, she collects various kinds of information on BSL-4 laboratories in the world to establish much secure environment of the National Research Center for the Control and Prevention of Infectious Diseases, Nagasaki University.

1. Okumura et al. *J Intl Health* 2019; 34(1): 35-43.
2. Delamou et al. *Lancet Glob Health* 2017; 5(4): e448-e457.
3. Camara et al. *Trans R Soc Trop Med Hyg* 2017; 111: 22-29.
4. Delamou et al. *BMJ Global Health* 2017; 2: e000202.
5. Delamou et al. *Afr J Reprod Health* 2017; 32(1): 104-113.

Associated Facility
**Central Research
 Laboratory**



Head and Professor
Shinjiro Hamano
 Senior Assistant Professor
Mihoko Kikuchi
 Assistant Professor
Miako Sakaguchi

The aim of the Central Research Laboratory is to efficiently operate and manage common equipments and to support general laboratory activities in the institute. In addition, this laboratory also supports research activities conducted in the institute by extramural investigators.

○**Molecular & Cellular Biology Unit**

Molecular & Cellular Biology Unit is responsible to maintain and operate following equipments located in the Central Research Laboratory; 16- and 48-capillary sequencers, GS junior genome sequencer and Mass Spectrometry-based Genotyping system for genome analysis; Flow Cytometer for cell function analysis; luminescence imager for visualization analysis; and Luminex Bead-array system and Fluorescence- Luminescence Multilabel Counter for multipurpose analysis. In addition, this unit is also responsible for maintaining the equipments/facilities to support general laboratory activities; such as Pure Water Supply, Ultracentrifuge, Lyophilizer, Speed-Vac, French Press, Bioruptor, Bead Crusher, sample storage in liquid nitrogen, Autoclave, dark room and cold room.

○**Light Microscope Unit**

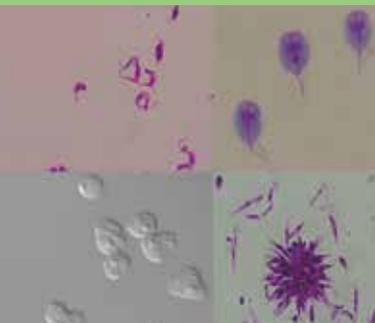
Light Microscope Unit provides optical

instruments to perform basic, translational, and clinical research on the imaging features of infectious diseases. We operate Nikon Infectious Disease Imaging Core laboratory established in April 2015. The laboratory has equipped Laser Scanning Confocal/Fluorescence Microscope (NIKON), Imaging Flow Cytometer (Luminex), Laser Scanning Confocal/Superresolution Microscope (ZEISS), and a Virtual Slide Scanner (Nanozoomer 2.0-RS, Hamamatsu Photonics).

○**Electron Microscope Unit**

Electron Microscope Unit supports ultrastructural characterization of microbial pathogens and the structural change of the pathogen-infected cells. This unit offers high quality imaging services by state-of-art techniques such as conventional and immuno-electron microscopy and 3D tomography, and also provides training on sample preparation and equipment usage. This unit is responsible for Transmission and Scanning Electron Microscopes (JEOL), Ultra-Microtomes (LEICA and REICHERT), vacuum coater, Hydrophilic Treatment Device, and Osmium Plasma Coater in addition to general laboratory facilities for a wide range application of electron microscopy.

Associated Facility
**NEKKEN Bio-Resource
 Center**



Project Representative, Professor
Osamu Kaneko
 Service Manager, Assistant Professor
Makoto Kazama

NEKKEN Bio-Resource Center (NBRC) was established in 2015 to take charge of National BioResource Project (NBRP) mission in Institute of Tropical Medicine (NEKKEN). NBRP constructs the framework for systematic collection, preservation, and distribution of bio-resources with a focus on those that required strategic development by the National Government. To promote life sciences it is important for researchers to share the various bio-resources necessary for pursuing researches and developments. NEKKEN has participated to NBRP services since 2002 when it was initiated by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and has been maintained by Japan Agency for Medical Research and Development (AMED) from 2015. We have been serving as Division of Protozoa in "Pathogenic Eukaryotic Microorganisms of a Core Facility Upgrading Program" under Medical Mycology Research Center (MMRC), Chiba University.

NBRC supports the research and education on pathogenic protozoa by providing following services; (1) web-based database of pathogenic protozoa maintained in Japan, including NBRC, with their owner

and strain information (2) acceptance of pathogenic protozoa for deposit, (3) preservation of protozoan strains, (4) distribution of a variety of protozoan strains, and (5) distribution of their microscopic specimens for education in academic organizations. To facilitate the collection, preservation, and provision of bio-resources, NBRC also implements the development of related technologies. Approximately 900 strains of pathogenic protozoa are preserved in NBRC, and approximately half of them are available to supply. Last year NBRC provided 69 protozoan strains to researchers and 88 strains were deposited to NBRC. Your cooperation and support to the project would be highly appreciated. Pathogenic protozoan resources available from NBRC are listed in the following website.

<http://www.tm.nagasaki-u.ac.jp/nbrc/>
 E-mail: protozoa@tm.nagasaki-u.ac.jp

Associated Facility
Neglected Tropical Diseases
Innovation Center
(NTDi Center)



Neglected
Tropical
Diseases
Innovation
Center

Director, Professor
Kenji Hirayama
Professor
Satoshi Kaneko
Professor
Tsuayoshi Kihara
Assistant Professor
Kota Yoshioka

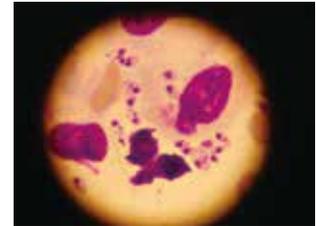
The Neglected Tropical Diseases (NTDs) are a group of infectious diseases that prevail in the tropical and poverty-stricken areas. They affect more than one billion people worldwide, resulting in prolonged poverty and economic hardship at both individual and geographical unit levels.

Ryutaro Hashimoto, then Japanese Prime Minister, kicked off the global parasite strategy to combat NTDs in 1998, so-called Hashimoto Initiative. The Initiative created the global momentum including various milestones; such as the NTD Roadmap in 2012, the International Public-Private Partnership, and the London Declaration for the mission to eradicate, eliminate and control 10 NTDs by 2020. Also, in May 2013, the World Health Assembly resolved the resolution WHA 66.12, expanding the NTD definition to 17 illnesses, which worked as another driver for active, global deployment of the initiative. 20 diseases are currently classified under NTDs, as of October 2018.

Since the Hashimoto Initiative rolled out,

Japan has been leading the G7 by supporting the core programs such as the Pacific Programme to Eliminate Lymphatic Filariasis (PacELF). As a national collaborative center for tropical medicine, NEKKEN has a mission to take the leadership role in research and development (R&D) to effectively eliminate or eradicate NTDs. To strengthen our mission, NEKKEN has established an in-house section "Neglected Tropical Diseases Innovation Center (NTDi Center)" in 2016, mandating to promote a project to utilize institutional excellence for developing innovative product and to search for appropriate funding organized by industry-academia-government partnership (PPP). To accelerate this activity, Center is supporting a hospital based cohort in Kenya to establish a drug vaccine trial site by PPP mechanism.

Center also initiated supporting activity to make a network between NTDs related organizations, institutions and researchers in Japan through maintaining an office of Japan Alliance on Global NTDs (JAGntd) since 2018.



Associated Facility
Office of Coordination
for Humanitarian Affairs



Section Chief, Professor
Taro Yamamoto

(Introduction)

In 2016, the Office of Coordination for Humanitarian Affairs was set up in our institute. Prof. Taro Yamamoto, who also heads the Department of International Health and Medical Anthropology, was nominated as the first chief of this section. One year has passed since its inception during which time we have dispatched missions to natural disaster affected areas and yellow fever epidemic areas.

(Aims)

The aims of this office are to provide support to both natural and manmade disaster areas. In order to undertake these missions, this office shall develop more human resources, do research, and become the center of an international humanitarian network.

(Organization)

1. Office of Coordination for Humanitarian Affairs was set up in NEKKEN
2. Appoint one section chief (professor)

(Past, Present and Future)

NEKKEN has dispatched missions to disaster afflicted areas such as Haiti in 2010,

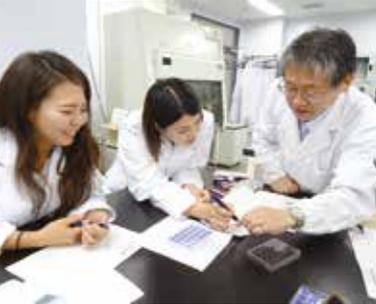
Tohoku region in 2011 just after the East Japan Great Earthquake, West Africa in 2014 and Nepal 2015. These activities make NEKKEN one of the leading organizations in Japan in terms of disaster relief activities.

Further, the infectious diseases team for Japanese Disaster Relief was decided in a cabinet meeting in October, 2015 based upon the fact that Ebola broke out in West Africa in 2014 and there was an international call for cooperation to help deal with it. NEKKEN is expected to serve as one of the main stakeholders in this field and was asked to participate on that team.

Because of all these events, setting up the Office of Coordination for Humanitarian Affairs was proposed.



Associated Facility Office for Training and Education



Head and Professor
Koya Ariyoshi
Assistant Professor
Momoko Yamauchi

The main role of our office is to run a short-course of tropical medicine, Training Course of Tropical Medicine (TTM). This course aims to support medical and co-medical personnel who plan to work in the tropics, by providing opportunities to learn a broad range of skills and knowledge relevant to practicing medicine, implementing disease control programs and conducting medical research in tropical and developing countries. The course began in 1978 and since 2016, it opens to the researchers who pursue technology for global health. Over 15 participants are accepted to attend the course in each year. As of the 43th course in 2020, 593 participants in total (including 207 medical doctors, and 376 co-medical such as veterinarian, nurses, community health nurses, midwives, pharmacists) from all over Japan have completed

the course. The course is run by the steering committee, which consists of members from both inside and outside the Institute of Tropical Medicine (NEKKEN).

During the thirteen weeks (April to June), the full-time staff members of NEKKEN and a substantial number of visiting professors and lecturers provide lectures, laboratory practical and field work, in the fields of virology, bacteriology, protozoology, parasitology, medical entomology, pathology, immunogenetics, epidemiology, human ecology, social medicine, clinical medicine and also geography and culture in tropics. Participants who successfully completed the course are awarded the Diploma in Tropical Medicine.



Admission ceremony in 2019

The clinical department of the Institute of Tropical Medicine (NEKKEN) was established in the Nagasaki University Hospital in 1967 and it has been locally known as "NEKKEN-NAIKA". Currently it runs an out-patient clinic twice a week as the Department of Infectious Diseases and provides in-patients care in a general internal medicine ward with 16 beds and a TB ward with 6 beds.

We are specialized in infectious diseases; we treat patients with systemic infectious diseases, including tropical infectious diseases, HIV/AIDS, tuberculosis, pneumonia, and other febrile cases. We receive approximately 500 - 600 consultation cases with suspected infectious diseases a year from other

wards. We also run a travel clinic for international travelers.

For training and education, we provide a number of lectures on infectious diseases to undergraduate students and bed-side training programs for resident physicians and infectious disease fellows. We organize a clinical case conference in English to make Japanese doctors prepared to work abroad. Staff doctors and resident doctors are regularly dispatched to hospitals in the tropics such as San Lazaro Hospital, the Philippines and the infectious disease ward in Bac Mai Hospital, Vietnam, MRC hospital in The Gambia, West Africa. That helps us to accumulate our knowledge and experience with clinical tropical medicine.

The University Hospital Infectious Disease Ward



Professor
Koya Ariyoshi
Associate Professor
Konosuke Morimoto
Senior Lecturer
Hiroto Yamanashi
Assistant Professor
Kensuke Takahashi
Assistant Professor
Mai Izumida
Assistant Professor
Kousuke Matsui



Group photo of staff members

Publications

Our official publications are as follows;

1. Bulletin of Nagasaki University Institute of Tropical Medicine (In Japanese, published yearly since 1964; PDF files are available at our web page.)



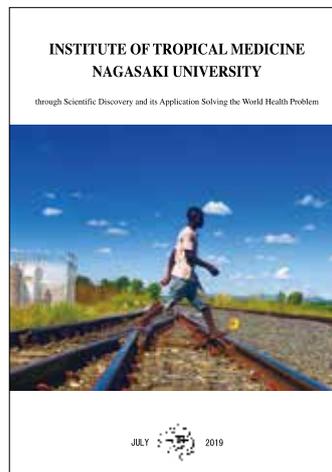
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2

2. Japanese Brochure (In Japanese, published yearly since 1977; PDF files are available at our web page.)

3. English Brochure: INSTITUTE OF TROPICAL MEDICINE NAGASAKI UNIVERSITY (This copy, published yearly since 1977; PDF files are available at our web page.)

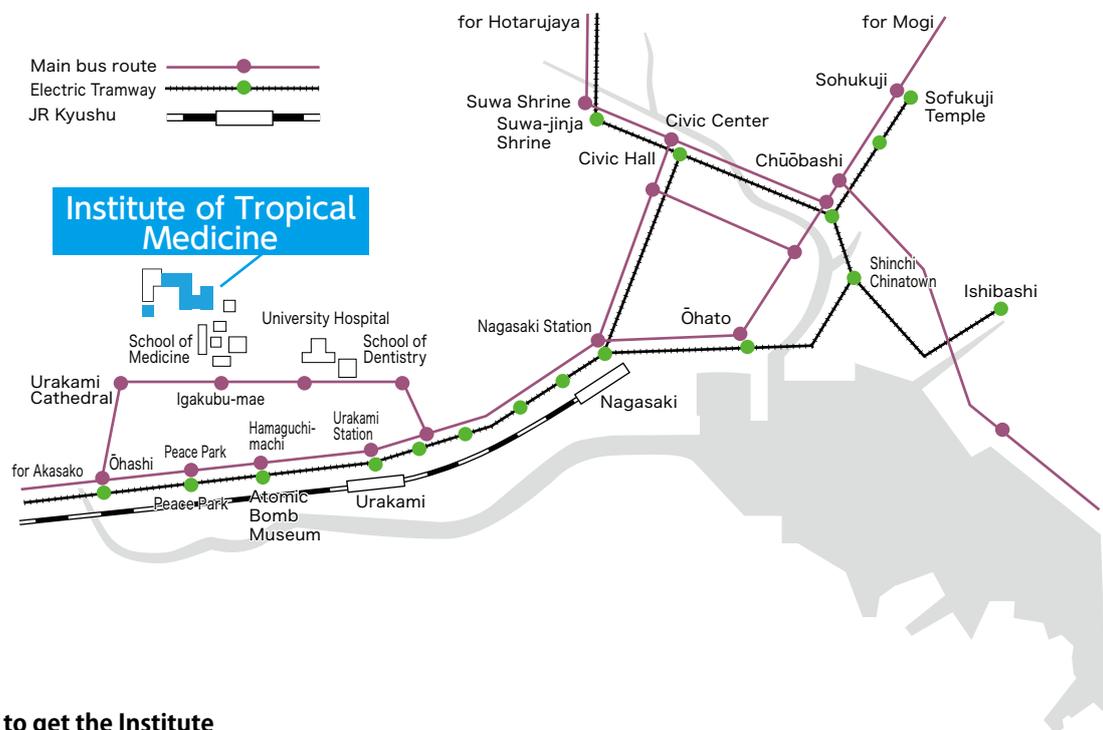


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4

4. Report of Nation-wide Cooperative Research Projects (Information on research activities and achievements as a nation-wide cooperative research center for tropical medicine is compiled.)



How to get the Institute

- From JR Nagasaki Station
 - ▶ Electric Tramway "Nagasaki Station" (bound for "Akasako") → "Atomic Bomb Museum" → about 10-minute walk
 - ▶ Nagasaki Bus "Nagasaki Station" (No.8 bound for "Shimoohashi" via "School of Medicine") → "School of Medicine"
- From JR Urakami Station
 - ▶ Electric Tramway "Urakami Station" (bound for "Akasako") → "Atomic Bomb Museum" → about 10-minute walk
- From Nagasaki Airport
 - ▶ Kenei Bus "Nagasaki Airport No.4" Bus Stop (For "Nagasaki Sta." (via "Showa-machi" / via "Showa-machi • Sumiyoshi")) → "Hamaguchi-machi" → about 10-minute walk



Nagasaki University

Institute of Tropical Medicine

Location 1-12-4 Sakamoto Nagasaki 852-8523

URL <http://www.tm.nagasaki-u.ac.jp/nekken/>

