# INSTITUTE OF TROPICAL MEDICINE NAGASAKI UNIVERSITY

through Scientific Discovery and its Application Solving the World Health Problem



#### **MISSION STATEMENT**

Institute of Tropical Medicine (NEKKEN), Nagasaki University

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, to strive for excellence in the following areas:

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



General View of the Institute

Coverpage: The Land Cruiser for research activity in Kenya Research station (in Suba District, Kenya)



#### **Preface**

The Institute of Tropical Medicine (NEKKEN), Nagasaki University, has a Global COE Program entitled Global Control Strategy of Tropical and Emerging Infectious Diseases. In the second year of our program, 2009, research efforts were fully launched by a total of 22 principal investigators (PIs). Our institute received approval by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) to continue to serve as one of the Collaborative Research Center on Tropical Disease in Japan in 2010 and onward.

NEKKEN, established in 1942, is a unique government-assisted institution for the research on tropical medicine, both in the basic and applied fields. Its reorganization led to the first collaborative institute in medical science in Japan in 1989, and designation as one of the Centers of Excellence in 1995 by MEXT. Present organization of the institute is composed of

3 major research fields (12 departments, 1domestic visiting department, 1 overseas visiting department), 4 centers, and 1 clinical unit.

NEKKEN set its General Goals: Mission Statement in May 1999. Diverse activities below are underway to achieve these general goals, with the indication of asterisk.

- \*Spear-head research in tropical medicine and international health
  - Strategic research activities have been conducted to develop new countermeasures against tropical diseases. These
    activities include analysis of base sequences of Japanese encephalitis and dengue virus genes, unraveling of structure
    and mechanism of host receptors for bacterial toxins, analysis of cell invasion by malaria parasites at molecular levels, and
    immunological analysis of tropical infectious diseases.
  - Epidemiological studies and research on malaria, dengue fever/dengue hemorrhagic fever, emerging viral infectious diseases, AIDS, acute respiratory infections, schistosomiasis, tropical infectious diseases, etc., in Southeast Asia, Eastern Africa, and other countries/regions.
  - 3. Environmental factors, such as vector and socio-economic problem, which cause the spread of tropical diseases in the developing countries have been studied.
- \*Global contribution through diseases control and health promotion in the tropics by applying the fruits of the research
  - 1. When the world was suffering from a severe outbreak of SARS in 2003, NEKKEN dispatched 3 researchers to P.R. China and other countries in respond to a request of WHO.
  - 2. And in 2005, NEKKEN dispatched the investigation team to make a survey of possible outbreak of infectious diseases in Indonesia and Sri Lanka, the countries that met disaster of tsunami. Thus the staffs have given their technical co-operation to disease control program in developing countries as WHO short-term consultants, JICA experts and other consultants.
- \*Cultivation of the researchers and specialists in the above fields
  - 1. NEKKEN offers training to graduate students (in doctor's and master's courses) through collaborative courses with Nagasaki University Graduate School of Biomedical Sciences (GSBS). In 2006, NEKKEN launched a one-year master's course in tropical medicine for MD students and in 2008, started to offer programs for students (capacity: 10) as an entity closely related to the master's course at Nagasaki University Graduate School of International Health Development (an independent graduate school).
  - 2. Since 1978. NEKKEN offers a 3-month course of Tropical Medicine and Related Studies.
  - 3. Since 1983, NEKKEN holds one year training course for foreign participants entitled Research in Tropical Medicine sponsored by JICA.
  - 4. Since 2006, by the cooperation of WHO/TDR, NEKKEN started Diploma Course on Research & Development of Products to meet Public Health Needs (3 weeks) which 6 universities in 4 countries (Japan, Thailand, China, and Colombia) cooperated to hold the course.

Based on the achievement mentioned above, in 1993, Department of Virology has been designated as WHO Collaborating Centre for Reference and Research on Tropical Viral Diseases, and since 2000 NEKKEN has played a role of core university in JSPS cooperative research program with Vietnam.

In 2003, NEKKEN and GSBS made a joint application to the 21st Century Center of Excellence (21c COE) Program supported by MEXT. Our research program Global Control Strategy of Tropical and Emerging Infectious Diseases successfully obtains a Government Grant of 5 years.

In 2005, the overseas research laboratories of NEKKEN has been established in Kenya Medical Research Institute (KEMRI), Nairobi, Kenya and National Institute of Hygiene and Epidemidogy (NIHE), Hanoi, Vietnam. In 2008, NEKKEN's proposal was approved as a Global COE Program, an advanced form of the 21st Century COE Program.

In March 2009, the institute staged an eight-day special exhibition entitled Africa's Nature, Development, and People – Nagasaki University Fighting against Tropical Infectious Diseases at the National Science Museum, Tokyo, which attracted over 10,000 visitors. A special open lecture, which was held as part of the exhibition, was attended by many participants.

In addition, the institute has a home page by which we appeal the public how tropical medicine is important for the well being of humankind and offer the information on the tropical diseases.

This pamphlet is one of our advocacy efforts to the public. It offers a brief but intelligible explanation on our research activities and other related social activities. Any suggestions and supports will be gratefully appreciated.

June, 2010 Kenji Hirayama M. D., Ph. D. Dean Institute of Tropical Medicine (NEKKEN) Nagasaki University

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#### **Historical Review**

The Institute of Tropical Medicine, Nagasaki University was originally founded in March 1942 as the East Asia Research Institute of Endemics, Nagasaki Medical College in order to perform basic and applied studies on endemic diseases in East Asia. At the beginning, most of its research activities were field studies conducted in mainland China by the Departments of Pathology, Bacteriology, Internal Medicine, and Dermatology of Nagasaki Medical College. August 9th, 1945, the atomic bomb was dropped in Nagasaki, and the Institute's all the facilities and research materials were completely destroyed together with Medical School. Consequently, the development of the Institute and its research activities had lagged significantly behind.

In April, 1946, the Institute changed its name to the Research Institute of Endemics, Nagasaki Medical College, and moved to Isahaya City in May to resume research activities. Yet in accordance with the National School Establishment Law issued in May, 1949, the Institute once again changed its name to the Research Institute of Endemics, Nagasaki University. In 1957, the Institute was affected by another disaster of massive flooding, and its facilities, equipment, and research materials were severely damaged. Thus, construction of a new building started in Sakamoto, Nagasaki City in 1960, and the Institute moved to the building in April of the following year. The Institute's Departments, which were only two at the time, Pathology and Clinics, increased its number every year after 1963, including Epidemiology, Parasitology, and Virology. The Sakamoto building finished its first expansion at the end of 1966.

In June, 1967, with the partial alteration of the National School Establishment Law, the name of the Institute was changed for the third time to the present one to carry out basic and applied studies on tropical medicine. Around the same time, the Department of Internal Medicine, Institute of Tropical Medicine, equipped with 20 beds, was opened in the University Hospital. In 1974, the Department of Bacteriology and the Reference Center were at-

tached, and in 1978, the Department of Preventive Medicine, consisting mainly of visiting professors, associate professors, and researchers, and the Tropical Medicine Training Course were launched. In the ensuing year, the Infectious Animals Deprivation Experiment Laboratory was promoted to become the Animal research Center for Tropical Infections, and the second building expansion was concluded in March, 1980. In September, 1983, a JICA-sponsored group training program Tropical Medicine Research Course was opened, the Department of Protozoology was established a year after, and the third building extension was finished in July the year after that. Two years later, the Department of Medical Entomology was created and the Institute was reorganized into the collaborative institute in another two years. In 1991, the Department of Biochemistry was added, and the fourth building expansion was ended in March, 1994. In April, 1994, the Institute was divided into three big Divisions, Tropical Microbiology, Pathogenesis and Clinical Sciences, and Environmental Medicine, with the establishment of two new research Departments, Thermal Adaptation and Social Environment, which have expanded to 12 Departments at present. The Institute was desig-nated as Center of Excellence in the forefront of scientific research in 1995, and a new research Department, Molecular Epidemiology, was established under the Research Field of Microbiology in 1996 to invite overseas visiting professors. In 1997, the Reference Room for the Tropical Medicine was replaced by the Tropical Disease Information and Reference Center, and it was again succeeded by the Research Center for Tropical Infectious Disease in 2001. In March, 2003, when the Sakamoto build-ing finalized its fifth expansion, its extension work of almost 40 years came to an end. In March, 2006, the main building's repair work was completed. In April, 2008, the Research Center for Tropical Infectious Disease for the Tropical Medicine was replaced by the Center for Infectious Disease Research in Asia and Africa and Tropical Medicine Museum. In June, 2009, the institute was authorized as the Collaborative Research Center on Tropical Disease by the Ministry of Edu-



# **Successive Deans of the Institute**

#### (East Asian Research Institute of Endemics)

**Susumu Tsunoo** May. 4, 1942 - Aug. 22, 1945

Kohei Koyano Dec. 22, 1945 - Jan. 23, 1948

**Kiyoshi Takase** Jan. 24, 1948 - Aug. 31, 1948

Noboru Tokura Sept. 1, 1948 - May. 30, 1949

#### (Research Institute of Endemics)

Noboru Tokura May. 31, 1949 - Aug. 31, 1958

Nanzaburo Omori Sept. 1, 1958 - Nov. 30, 1963

Hideo Fukumi Dec. 1, 1963 - May. 31, 1967

### (Institute of Tropical Medicine)

Hideo Fukumi June. 1, 1967 - Nov. 30, 1969

Daisuke Katamine Dec. 1, 1969 - Nov. 30, 1973

Kaoru Hayashi Dec. 1, 1973 - Nov. 30, 1977

**Tatsuro Naito** Dec. 1, 1977 - Nov. 30, 1979

Daisuke Katamine Dec. 1, 1979 - Apr. 1, 1981

Keizo Matsumoto Apr. 2, 1981 - Apr. 1, 1991

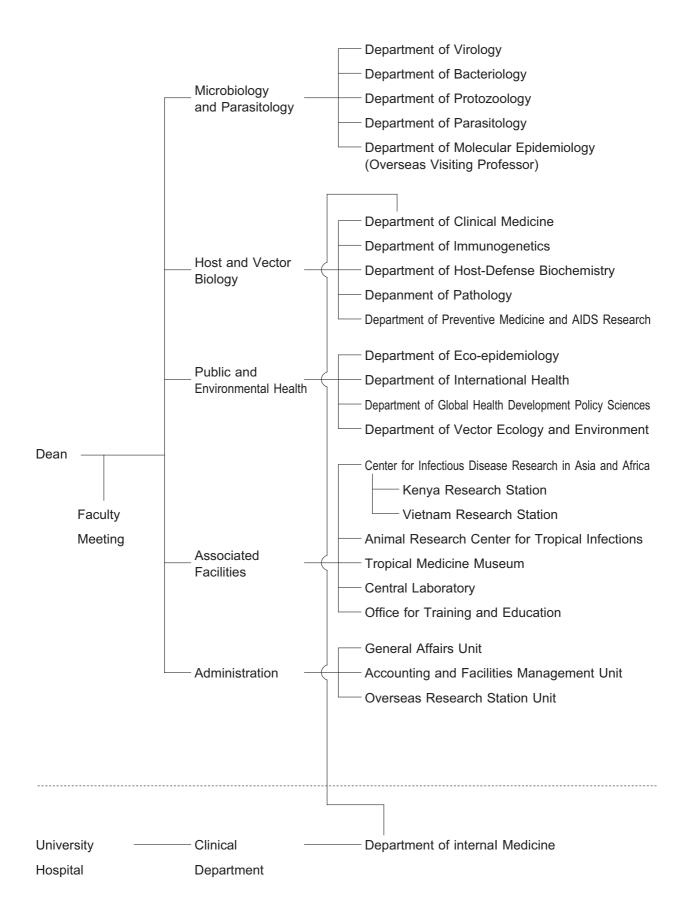
Mitsuo Kosaka Apr. 2, 1993 - Apr. 1, 1997

Akira Igarashi Apr. 2, 1997 - May. 31, 2001

Yoshiki Aoki Apr. 1, 2001 - May. 31, 2007

Kenji Hirayama Apr. 1, 2007 - Up to the present

# Organizational Chart



# **Research Center on Tropical Diseases**

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

#### (1) The Goal of the Center

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

The Tropical Infectious Diseases have been spreading in the tropical area, which is the reflection of environment and socio-economic situation existed there. It is considered to be a big challenge related to health. As a matter of fact, emerging and re-emerging infectious diseases including newly emerging infectious diseases, HIV and tuberculosis have been spreading globally with tropical area being its epicenter. The tropical area is not only the battle field where we, human being, fight against them but also the experimental ground where we newly create and develop our knowledge and technology alike in order to control infectious diseases.

The Research Center on Tropical Diseases is

to accomplish with the members in the diverse scientific communities collaborative researches rooted upon the field where infectious diseases are prevailing, making use of the facilities like Asia and Africa Research Stations internationally recognized. It also serves as a resource center for information and biological samples related to infectious diseases speeding globally.

#### (2) Outline of the Collaborative Research

The Research Center on Tropical Medicine appeals to the public for the collaborative research, which is either basic or applied research based upon epidemiological, clinical or public health framework.

The Research Center on Tropical Medicine appeals to the public for the research meeting, which promotes and facilitates the research of infectious diseases through exchanging information or technologies necessary.

The Research Center on Tropical Medicine is also to deliver bio-resources including infectious agents, information, and etc. collected and stored here, and thus serves as a resource center on Tropical Medicine.

#### (3) Organizational Chart of the Center

As for administration of this research center, the dean of the Institute of Tropical Medicine established the Steering Committee for the Collaborative Research Center on Tropical Medicine, which was composed of 10 members, out of whom more than half should be out side the

university concerned. The Steering Committee for the Collaborative Research Center on Tropical Medicine is responsible for adoption of the applications and monitoring and evaluation of the activities in question.

In order to support activities above mentioned, the specific Section supporting the Research Center on Tropical Medicine was newly formed and a professor was designated to be a section chief.

#### (4) Activities in 2009

There was 33 applications for collaborative researches, out of which 25 was adopted.

There was 5 applications for research meeting, out of which 5 was adopted.

There was 3 applications for collaborative researches specified research area, out of which 3 was adopted.

# The Steering Committee for the Collaborative Research Center on Tropical Medicine

#### **Committee Member outside the university**

National Reseach Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine

Professor Ikuo Igarashi

Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association

Director Nobukatsu Ishikawa

Center for Integrated Area Studies, Kyoto University

Professor Fumiko Oshikawa

Department of Tropical Medicine and Malaria Research Institute National Center for Global Health and Medicine

Director OShigeyuki Kano

National Institute of Infectious Diseases

Deputy Director-General Ichiro Kurane

RIKEN Center of Research Network for Infectious Diseases

Director Yoshiyuki Nagai

Committee Member outside the institute

Graduate School of Biomedical Sciences Professor Osamu Nakagomi

Graduate School of Biomedical Sciences Dean Shunichi Yamashita

**Committee Member inside the institute** 

Institute of Tropical Medicine Professor Toshiya Hirayama

Institute of Tropical Medicine Professor Koya Ariyoshi

Institute of Tropical Medicine Professor Taro Yamamoto

©: Chairman

# Character of research organization and activities

Based on the following research organization and intimate linkages with other research institutes and universities, the institute aims at accomplishing a mission Spear-head research in tropical medicine and international health.

- To study comprehensively the tropical diseases which are raging in the developing countries, research organization of the institute consists of 3 major research fields which deal with the classical triadof human-agent-environment determinants of infectious diseases and Overseas Research Station, Animal Research Center for Tropical Medicine, and Tropical Medicine Museum. Other facilities of the institute include a joint research laboratory and a tropical medicine education office.
- The research of tropical medicine faces the inevitable fact that the bench is in the bush. Therefore the institute has a close linkage with the overseas institutes in Asia, Africa and South Americas and continues the joint studies. Memorandums of academic exchange programs were signed between Nagasaki University and 8 overseas institutes. Since the overseas research laboratories of the institute has been established in Kenya Medical Research Institute (KEMRI), Kenya and National Institute of Hygiene and Epidemiology (NIHE) Vietnam in 2005, by the grants from Ministry of Education, Sports, Culture, Science and technology (MEXT), the extensive and longitudinal studies on tropical diseases has been on the progress, and are extended to continue in more 5 or 6 years. The exchange program under the core university system of JSPS established between NEKKEN and NIHE in Vietnam in 2000 has been renewed in 2005 and completed in 2009.
- The prevalence of tropical diseases depends on the geographic, social and economic factors. Therefore the institute has established the special research system which helps forward the multidisciplinary studies on tropical diseases.

#### **Graduate Courses**

In April, 2002, the structure of doctoral course in Nagasaki University was re-organized; three Graduate Schools of Medical Science, Dental Science and Pharmacology were integrated into the

Graduate School of Biomedical Sciences. The school now runs four doctoral courses. All the departments in the Institute of Tropical Medicine (NEKKEN) belong to the Course of Infection Research. Students who wish to apply for the doctoral course under the supervision of the ITM, are requested to contact the professor of department where he or she wishes to study, prior to the submission of application form to the office of the Graduate School.

#### < Master of Tropical Medicine (MTM)>

In April, 2006, the Nagasaki University graduate school of Biomedical Sciences opened the Master of Tropical Medicine (MTM) course, which accommodates 12 students from various countries. The curriculum consists of three parts: (1) 4 months intensive lecture and practice on Clinical Tropical Medicine and Tropical Public Health, followed by 2 weeks oversea group training on tropical clinical medicine and public health in Thailand, and (3) 6 months dissertation preparation for each student's subject. Degree of Master of Tropical Medicine is awarded to successful students. The applicant should have more than two years of clinical experience as a medical doctor, and should have sufficient communication skill in English.

#### < Master of Public Health (MPH)>

In April, 2008, the Graduate School of International Health Development was founded at Nagasaki University. The main aim is to cultivate specialists who contribute to the promotion of good health in developing countries. A Master of Public Health (MPH) degree is awarded to students who successfully complete this two-year course. Since tropical medicine plays a pivotal role in promoting good health internationally, four professors from NEKKEN serve as a full-time faculty member in the program. The applicants are required to have sufficient command of Japanese language.

The information on these courses including application from is available through our homepage. http://www.tm.nagasaki-u.ac.jp/nekken/english/index.html

# Three-month Course on Tropical Medicine

This is a short-course of tropical medicine. This course aims to support medical and comedical personnel who plan to work in the tropics, by providing opportunities to learn a broad range of skills and

knowledge relevant to practicing medicine, directing disease control programs and conducting medical research in tropical and developing countries.

The course began in 1978. As of the 32nd course in 2009, 381 participants (including 149 medical doctors, and 232 comedical such as nurses, community- health nurse, midwives, pharmacist) from all over Japan have completed the course. Fifteen participants are accepted to attend the course in each year. The course is run by the steering committee, which consists of members from both inside and outside the Institute of Tropical Medicine (ITM).

The full-time staff members of the ITM and a substantial number of visiting professors and lecturers provide the 14 weeks (June to August) of lectures, laboratory practicals and field work in the field 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 completed the course successfully are awarded the Diploma in Tropical Medicine.



Admission ceremony in 2009

# Clinical Medicine and Research for Tropical Doctors (JICA Training Program)

As a part of Japan Government Technical Cooperation Programs for contributing to upgrading the levels of tropical medicine research, to improving medical standard, and to promoting friendly relations to the developing countries, this training course was established in 1983, in collaboration with the Japan International Cooperation Agency (JICA). As of 2009, the ITM has trained 206 trainees from 49 countries in Asia, Africa, Latin America etc.

The objective of this course is to provide

trainees with various opportunities to enrich their basic knowledge and practical techniques for controlling endemic and epidemic diseases and conducting medical research to improve various medical problems in their countries in the tropics.

Up to 2005, the ITM has accommodated 5-10 trainees per year. Each trainee belongs to a host department where they conduct their research and receive a Diploma from the ITM.

Since April 2006, this training course was formally incorporated into Master of Tropical Medicine course of the Graduate School of Biomedical Sciences, Nagasaki University and students have received higher education in quality.

#### **Public Communication**

Lectures and film shows for citizens are held occasionally. Every year, several groups of high school students with teachers visit our museum, attending lectures and film shows. To accumulate know-how of risk communication on tropical infectious diseases in our institute, we are planning to introduce science cafe sessions where we have frank communication with citizens on the present state and future prospects of research on tropical medicine.

#### **Publications**

Our official publications are as follows;

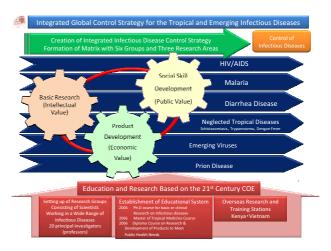
- 1) Bulletin of Nagasaki University Institute of Tropical Medicine (in Japanese, yearly since 1964, PDF files are available at our Web page.)
- English Brochure: INSTITUTE OF TROPICAL MEDICINE NAGASAKI UNIVERSITY (this copy. Yearly since 1977, PDF files are available at our Web page.)
- 3) Japanese Brochure (in Japanese yearly since 1977, PDF files are available at our Web page.)
- 4) Report of Nation-wide Cooperative Research Projects (Information of research activities and achievements as a nation-wile cooperative research center for tropical medicine is compiled.)

# Global COE Program Integrated Global Control Strategy for the Tropical and Emerging Infectious Diseases

The United Nations issued eight development goals in its Millennium Declaration in 2000 as international targets, with the core message being measures against infectious diseases expressed as follow: Stop the occurrence of major diseases including HIV/AIDS by 2015 and decrease the subsequent incidence rate. The ultimate goal of this program is to control and conquer these major infectious diseases. We will further advance and internationalize our outstanding achievements in the 21st century COE program to create a new center of excellence (COE) toward the accomplishment of these objectives.

For controlling and overcoming infectious diseases, tactical strategies and personnel with appropriate skills to carry them out are absolutely necessary. This new COE will focus on neglected infectious diseases (dengue fever, schistosomiasis, etc.), which have rarely been considered because most of the cases have been happened in poor

developing countries, plus diseases involving diarrhea, which tend to be treated as curable in developed countries. Of these tropical and emerging infectious diseases, we will lay concepts of a new strategy in a comprehensive manner to control and overcome those diseases which have currently become global issues or major impediments to development, and work on research and development of innovative technology essential for the implementation of our strategy. Moreover, through this process, we will foster promising experts who can play a leading role in the future of this research area.



#### Member

		Affiliation	Speciality	Research Theme	Assistant Professor /Post Doctor Fellow
	Osamu Nakagomi	Graduate School of Biomedical Science (GSBS)	Molecular Epidemiology	Diarrhea	
	Osamu Kaneko	NEKKEN	Medical Protozoology	Malaria	Miako Sakaguchi
	Toshiya Hirayama	NEKKEN	Bacteriology	Diarrhea	Masayuki Nakano
Basic	Noriyuki Nishida	GSBS	Cellular and Molecular Biology	Prion	Kazunori Sano
Research	Katsuyuki Yui	GSBS	Immunology	Malaria	Takahiko Tamura
	Toshifumi Matsuyama	GSBS	Cytokine Signaling	HIV/AIDS	Yuhua Ma (China)
	Shinjiro Hamamo	NEKKEN	Medical Helminthology	Negglected Tropical Infections (NTD)	Keishi Adachi
	Kouichi Morita	NEKKEN	Molecular Virology	Arbovirus/Virus	Daisuke Hayasaka
	Tetsu Yamashiro	NEKKEN	MicroVirology	Vietnam Reserch Station	
	Noboru Minakawa	NEKKEN	Vector Ecology and Environment	Vector Control/Malaria	
E: 11 D	Satoshi Kaneko	NEKKEN	Eco-epidemiology	Kenya Reserch Station /Social Technology	Yoshito Fujii
Field Based Research	Taro Yamamoto	NEKKEN	International Health	Social Technology	Katsuyuki Eguchi
rescaron	Koya Ariyoshi	NEKKEN	Clinical Tropical Medicine	HIV/AIDS	Naho Tsuchiya
	Hiroyuki Moriuchi	GSBS	Paediactrics	HIV/AIDS	
	Kenji Hirayama	NEKKEN	Immunogenetics	NTD /Product Development	Mohammed Nasir (Nigeria)
	Akira Kaneko	NEKKEN	Malariology	Malaria	
	Takashi Ito	GSBS	Biochemistry	Product Development	
	Masayuki Ikeda	GSBS	Pharmaceutical Medicine	Product Development	
	Masaaki Kai	GSBS	Chemistry of Biofunctional Molecules	Product Developmentt	Zhang Huan (China)
Product Development	Nobuyuki Kobayashi	GSBS	Molecular Pharmacology of Infectious Agents	HIV/AIDS	Hiroaki Kawano
	Shigeru Kohno	GSBS	Clinical Microbiology and Immunology	Product Development	Taiga Miyazaki
	Koji Nakayama	GSBS	Microbiology and Oral Infection	Product Development	Tomoko Kadowaki
	Hitoshi Sasaki	University Hospital	Hospital Pharmacy	Product Development	Tomoaki Kurosaki
	Naoki Yamamoto	NEKKEN	Virology	Product Development	
Education					Hikaru Sato
Education					Tomoko Abe

# **Department of Virology**

This Department has been conducting basic and applied research on mosquito-borne flaviviral diseases such as Japanese encephalitis (JE), dengue fever (DF)/dengue hemorrhagic fever (DHF), as well as SARS virus.

# Analysis on the structure and function of JE and dengue viral genome

Nucleotide sequence analysis and molecular expression of JE and dengue viral genome have been carried out together with long PCR techniques in order to study molecular epidemiology, epitope analysis, biological activity of nonstructural proteins, and virulent viral gene responsible for viral pathogenesis.

# Analysis on apoptosis induced by flavivirus infec-

Flavivirus infection induces apoptosis of the infected cells. Characterization of apoptosis and its relation to pathogenecity has been studied in cell line and animal model.

# Development of rapid diagnosis of flaviviral diseases

Viral genome detection and identification by PCR and LAMP methods, preparation of diagnostic antigen from infected cell culture fluid, and simplification of IgM antibody detection have been carried out.

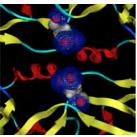
#### Research on emerging viral infectious diseases

Studies on the development of diagnostic methods and epidemiology on SARS virus, Nipah virus and H5N1avian influenza virus have been conducted in Viet Nam and other countries in the South East Asia.

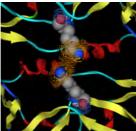
#### Activities as a WHO Collaborating Center

Dr. S. T. Han, then Regional Director of WHO Western Pacific Region (WPR) designated the Department of Virology, Institute of Tropical Medicine, Nagasaki University as a WHO Collaborating Center for Reference and Research on Tropical Viral Diseases on 23 Nov. 1993. In 2003, epidemiological and virological studies on

VnHcm18/02-C 62 Glu



VnHcm18/02-K 62 Lys



One specific amino acid change of Dengue virus surface protein affect its cell tropism.

SARS were added to its research activities. The Department was redesig-nated as a WHO Collaborating Center for Reference and Research on Tropical and Emerging Virus Diseases on 3 Feb. 2008 by Dr. Shigeru Omi, former Regional Director of WHO/WPR. The Department has received WHO fellows from Vietnam, Fiji, and the Philippines, and dispatched WHO short-term consultants on the activities relevant to its terms of reference. Dr. Kouichi Morita was dispatched to WHO/WPRO and was appointed as Reginonal Adviser on Communicable Diseases for the Western Pacific Region from 16 May 1995 to 15 May 1998. Dr. Futoshi Hasebe was dispatched to the WHO Western Pacific Regional Office to collaborate in the global emerging infectious disease control program from March 2004 The Department initiated and to March 2006. held the First GOARN National Training Course by WHO/WPRO and Nagasaki University in Nagasaki, Japan, from 25 to 29 February 2008 in collaboration with WHO/WPRO.

Professor Professor Professor (Project) Assistant Professor Assistant Assistant Assistant Assistant Assistant Graduate student Graduate student

Kouichi Morita Tetsu Yamashiro Futoshi Hasebe Shingo Inoue Toru Kubo Yu Fuxum Takeshi Nabeshima Daisuke Hayasaka Genichiro Uechi Kozue Hotta Kazumi Jodai Masaaki Kawazoe Miki Masuda Takako Chiba Avumi Sashikata Guillermo Posadas Herrera Dinh Tuan Duc Lyre Anni Espada Murao Nauven Dong Tu Kenta Okamoto Akira Yoshikawa Mya Myat Ngwe Tun Muhareva Raekiansyah Yuki Takamatsu



P3 level laboratory

# **Department of Bacteriology**

Our major research interest is to elucidate the etiologic agents isolated from pathogenic bacteria related to the worldwide emerging and reemerging diseases and to know the virulence mechanisms of bacterial pathogens.

Helicobacter pylori is a bacterial pathogen found in the stomach mucosa of more than 50% of the world population and more common (over 80%) in developing and tropical countries. Infection with H. pylori plays a major role in the development of chronic gastritis and peptic ulcer, and is a risk factor for gastric cancer. Pathogenic strains of H. pylori secrete a potent protein toxin, a vacuolating cytotoxin, termed VacA, which causes progressive vacuolation of epithelial cells and gastric injury. We found that VacA induces multiple effects on epithelial cells, including mitochondrial damage [1] and apoptosis [2]. These actions of VacA appear to result from activation of cellular pathways, independent of those leading to vacuolation. Similarly, VacA-induced phosphorylation of G proteincoupled receptor kinaseinteractor 1 (Git 1), which may be responsible for epithelial cell detachment caused by VacA, leading to peptic ulceration [3], and VacA-induced activation of p 38/ATF-2- mediated signal pathway [4] are independent of VacA effects on cellular vacuolation.

Analysis of VacA receptors provided new insights into the molecular basis of VacA function. We reported that two VacA proteins, termed m 1 VacA and m 2 VacA, which were defined by sequence differences in the middle of the molecules, interacted with target cells by binding to two types of receptorlike protein tyrosine phosphatases (RPTPs), i. e., RPTP $\alpha$  and RPTP $\beta$ , resulting in toxin internalization and vacuolation of the human gastric adenocarcinoma cell lines AZ-521 and G 401 [5, 6, 7]. By analysis of the pathological responses of wild type and RPTPβ-deficient mice to oral administration of VacA, we found that RPTPβ functions as a receptor for VacA and produces the disease associated with VacA toxicity including gastritis and gastric ulcer [3]. Receptor-dependent translocation of VacA to lipid

Lipid rafts

Plasma membrane

CagA

Inhibition of p21 Expression

Reptipa

Plasma membrane

CagA

Inhibition of p21 Expression

Reptipa

Plasma membrane

CagA

Inhibition of p21 Expression

Reptipa

Activation of Calcineum

Nucleus

Millochondrial

Damage

Apoptosis

Apoptosis

Cox-2

Cell growth

Virulence mechanism of Helicobacter pylori vacuolating cytotoxin, VacA.

rafts is critical for signaling pathways leading to it's toxicity [8, 9, 10].

To further elucidate the potential mechanism of how H. pylori establishes infection, we also investigate the hostparasite relationships of H. pylori, focusing on VacA as well as CagA, which is an effecter protein injected by its type IV secretion system into host cells. Consistent with suppression of nuclear translocation of nuclear factor of activated T cells, NFAT, in Jurkat T cells, VacA counteracted CagA-induced activation of NFAT in AGS cells, suggesting that the two major *H. pylori* virulence factors inversely control NFAT activity [11]. Deregulation of NFAT, either positively or negatively, may contribute to cellular dysfunctions that underlie diverged clinical manifestations caused by H. pylori infection. In addition, VacA activates the PI3K/Akt signaling pathway, resulting in phosphorylation and inhibition of GSK3β, and subsequent translocation of βcatenin to the nucleus, consistent with effects of VacA on β-catenin-regulated transcriptional activity, suggesting the possibility that Wnt/β-catenin dependent signaling might play a role in the pathogenesis of H. pylori infection, including the development of gastric cancer [12].

References: [1] Microb. Pathog. 31:29-36, 2001, [2] J. Biol. Chem. 281: 11250-11259, 2006, [3] Nat. Genet. 33: 375-381, 2003, [4] J. Biol. Chem. 279: 7024-7028, 2004, [5] J. Biol. Chem. 278:19183-19189, 2003, [6] J. Biol. Chem. 279: 51013-51021, 2004, [7] Cell Microbiol 7: 1285-293, 2005, [8] Infect Immun. 74, 6571-65 80, 2006, [9] Intect. Immun. 75:4472-4481, 2007, [10] J. Immurol. 180: 5017-5027, 2008, [11] Proc. Natl. Acad. Sci. USA. 102: 9661- 9666, 2005. [12] J. Biol. Chem. 284:1612-1619, 2009

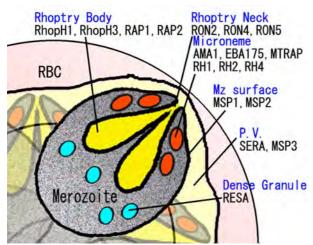
Professor Senior Assistant Professor Assistant professor Assistant professor Technologist COE Technician Assistant Toshiya Hirayama Akihiro Wada Masahiko Ehara Masayuki Nakano Mamoru Iwami Asami Fujii Misuzu Hashiguchi



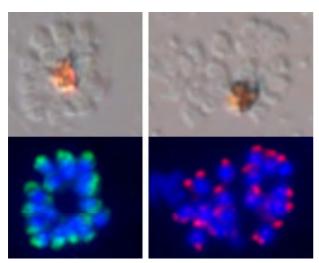
Laboratory

# **Department of Protozoology**

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 fundamental aspects of the parasite's life cycle, such as the mechanisms behind erythrocyte invasion and the phenomenon of cytoadherence of parasite-infected erythrocytes. In addition, we are also conducting research aimed at elucidating the intracellular survival strategy of Trypanosma cruzi.



Schematic of the malaria merozoite and its invasionrelated molecules.



Newly identified malaria proteins were localized to the apical end of the merozoites. Blue is parasite nucleous, green and red are the location of the identified proteins. Upper panels are DIC images of the malaria parasite.

We are actively pursuing the following lines of investigation:

#### 1. Malaria

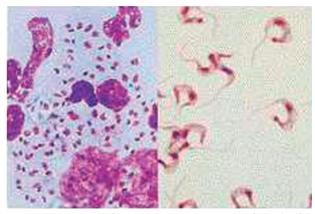
- The molecular basis of host cell invasion by parasites
- 2) The molecular basis of cytoadherence of parasite-infected erythrocytes
- 3) Transcriptional control in malaria parasites
- 4) How different malaria parasite species interact in the host
- 5) Recrudescence of malaria parasites
- 6) Molecular epidemiology of *P. falciparum* malaria in endemic countries
- Prevalence, origins and population genetics of African Plasmodium vivax
- 8) Transmission dynamics of *P. knowlesi*, a zoonotic monkey malaria parasite

#### 2. Trypanosoma

- 1) The function and expression mechanism of trans-sialidase
- 2) Stage specific adaptation mechanisms employed by different *Trypanosoma* species

Professor Senior Assistant Professor Assistant Professor Assistant Professor Assistant Professor Assistant Professor Assistant Assistant Assistant Assistant **Graduate Student Graduate Student** Graduate Student **Graduate Student Graduate Student Graduate Student Graduate Student** Visiting Researcher Visiting Researcher Visiting Researcher Visiting Researcher Visiting Researcher Visiting Researcher

Osamu Kaneko Haruki Uemura Shusuke Nakazawa Kazuhide Yahata Richard Culleton Miako Sakaguchi Miki Kinoshita Nozomi Hayashida Yuko Ichimaru Sheng Paul Su Akikocristina Salati Morakot Kaewthamasorn Jean Seme Fils Alexandre Xiaotong Zhu Megumi Inoue Takaya Sakura Phonepadith Xangsayarath Jianxia Tang Ning Jiang Sofia Trindade Borges Yahui Lin Gege Wang Tippawan Sungkapong



Amastigotes (left) and trypomastigotes (right) of *Trypanosoma cruzi*.

# **Department of Parasitology**

Infectious Diseases are still a huge menace to human health and continue unabated in tropical areas under conditions of poverty and the unique natural and social environments. Many parasitic diseases infect humans for long periods of time without killing them, giving rise to tremendous 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.

#### Target diseases of our studies

We have been carrying out both field and laboratory studies on several of the most important helminthic diseases, including schistosomiasis, filariasis and intestinal helminthiasis and on important but neglected protozoan diseases such as amoebiasis, leishmaniasis and trypanosomiasis.

#### 1) Schistosomiasis and Filariasis

Since 1981, the research project on *Schistosoma* haematobium has been carried out in Kwale, Kenya, in cooperation with Kenya Medical Research Institute (KEMRI). This year, we are going to start a new research project on parasitic diseases there and to examine cercarial concentration of *S. haematobium* in natural water and the ecology of *Bulinus globosus*, an intermediate host of *S. haematobium*, and then to try to prevent transmission through snail control. Inhabitants' water contact and their knowledge, attitude and practices (KAP) about the infection will also be studied. In the laboratory, we have been maintained *S. mansoni*, *S. haematobium*, and several spices of intermediate snails.

A research project on filariasis was carried out in Kwale, Kenya, in cooperation with KEMRI between 1990 and 1996. Transmission potential and morbidity were studied. In the laboratory, *Brugia malayi*, *B. pahangi* and the vector mosquito, *Aedes aegypti* have been maintained for many years.

#### 2) Amoebiasis, Leishmaniasis, Trypanosomiasis etc.

Genetic epidemiology and cohort studies on amoebiasis and leishmaniasis are carried out in cooperation with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B.) and the University of Virginia. Field sites include Dhaka and rural areas of Bangladesh. In addition to genetic factors, we aim to elucidate various environmental factors that determine and/or influence the outcome of the infection. In the laboratory, we study host defense mechanisms against *Leishmania major*, *L. donovani* 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. After we developed animal models of intestinal amoebiasis together with Prof. Houpt at University of Virginia, we are now devoting ourselves to the study of pathogenesis of *Entamoeba histolytica* and host defense mechanisms to *E. histolytica*.

# 3) Cohort study using HDSS on infectious diseases in Mbita area (the eastern lakefront of Lake Victoria)

We have started cohort study of infectious diseases in Mbita area using HDSS (Health and Demographic Surveillance System). This HDSS has been established and maintained in Suba area in Kenya. This year, the feasible studies on shistosomiasis, other helminthic and protozoan infections, HIV/AIDS, tuberculosis and so on are going to be carried out.

Shiniiro Hamano Professor Assistant Professor Yoshinori Mitsui Assistant Professor Kentaro Kato **Graduate Student** Chikako Shimokawa **Graduate Student** Shumpei Kambe **Graduate Student** Yombo Dan Justin Kalenda Technologist Mitsumasa Miura Assistant Masako Hayashida Assistant Satomi Tominaga Assistant Fumie Hara



One of our field site in Nepal, South Asia

# **Department of Clinical Medicine**

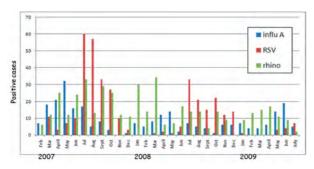
Main targets of research activities in the Department of Internal Medicine are tropical infectious diseases, respiratory infectious diseases and HIV/AIDS, all of which causes severe disease burden in the tropics. We conduct various basic scientific research using animal models in Nagasaki and clinical epidemiology research in the oversea through international collaboration. Specific research activities are described as follows:

#### 1. Respiratory Infections

Our goal is to better-understand mechanisms causing severe and treatment-refractory pneumonias at molecular levels toward development of a novel treatment strategy. We hypothesize that patients with severe and treatment-refractory pneumonia has an impaired process in inducing the cessation of inflammation and re-construction of damaged tissues. We, particularly, focus on the function of macrophage which is responsible for clearing apoptotic cells from the inflammation site using a mouse pneumonia model. We have also developing a rapid and comprehensive assay to identify multiple pathogens causing respiratory infections and an assay to quantify bacterial load, which are being applied for several clinical studies in and outside Japan.

#### 2. Pediatric Infectious Diseases in Vietnam

We have, so far, conducted studies on clinical and bacteriological diagnosis, antimicrobial susceptibility and molecular epidemiology in collaboration with National Institute of Hygiene and Epidemiology. Since 2005, we started a large-scale of census survey targeting all residents in Nha Trang city and its adjacent Nin Hoa district in the middle part of Vietnam. During the census, we also collected information regarding environment and diseases burden (particularly pneumonia, diarrhea, dengue fever), health utilization pattern. Since 2006, a research clinician has been dispatched from our department and monitoring all pneumonia cases admitted to the pediatric ward at Kan Hoa General Hospital in the above city. So far over 2,000 pneumonia cases have been registered and we demonstrated that environmental tobacco exposure is a risk factor for child pneumonia admission. We also determined pathogen specific incidence rates and demonstrated seasonality of respiratory infection in Vietnam. In 2009, we commenced a birth cohort study, recruiting 2,000 pairs of mothers and new-born babies, with the objective of facilitating mother-to-child transmission studies of various infections and stud-



Numbers of pneumonia children admitted to the Khan Hoa Hospital

ies of host-gene polymorphisms associating the severity of pediatric infectious diseases.

#### HIV cohort studies in northern Thailand

In collaboration with National Institute of Health. Thailand and National Institute of Infectious diseases, Japan, a large scale of cohort study targeting HIV-infected individuals and their spouses has been established and maintained in Lampang Hospital. northern Thailand. So far, neraly 2000 people have participated. The main objectives of this cohort are to understand mechanisms of resistance to HIV infection among HIV-exposed but uninfected spouses living with HIV-infected patients and mechanisms of slow-progression among HIV-infected slowprogressors. These studies are being conducted in close collaboration with Thai counter parts and international experts in various fields such as hostgene polymorphisms, molecular immunology, molecular epidemiology and virology. Furthermore, based on this field setting, we are also conducting studies on frequencies of opportunistic infection, the effect of anti-retroviral drug therapy, and social need for children born to HIV-affected parents.

Department of Clinical Medicine

Professor Associate Professor Associate Professor Assistant Professor Assistant Professor Assistant Professor Assistant Professor Research Associate Visiting Professor COE Research Fellow COE Research Fellow Postdoctoral Fellow Assistant Assistant Assistant Graduate student Graduate student

Koya Ariyoshi Konosuke Morimoto Laymyint Yoshida Kei Miyagi Hiroshi Yoshino Hikaru Sato Motoi Suzuki Kiwao Watanabe Tomoyuki Maekawa Naho Tsuchiya Tomoko Abe Wolf-Peter Schmidt Mitsuyo Kirie Rina Shiramizu Rika Nogawa Vu Thi Thu Huong Masahiko Mori Yoko Tsumori Yoshirou Yamashita Kazuhiko Koyama Tohru Ogasawara Yusuke Shimakawa Sugihiro Hamaguchi Kensuke Takahashi Reiko Miyahara Le Nhat Minh Takayuki Oike



At the Khan Hoa General Hospital (Vietnam)

# Clinic at the University Hospital

The Department of Clinical Medicine is the only one clinical department at the Institute of Tropical Medicine. It has a clinic and a medical ward with about 17 beds on the 11th floor of the Nagasaki University Hospital. We specialized in the Infectious Diseases and Respiratory Diseases; diseases that we handle are systemic infectious diseases, including tropical infectious diseases and HIV/AIDS, tuberculosis and pneumonia, and various neoplasmic and inflammatory respiratory diseases. We actively receive consultations regarding diagnosis and management of infectious diseases from other departments. Each year approximately 200 to 300 cases are referred to our department. The outpatient clinic is open two days a week for treating patients with respiratory diseases and infectious diseases. In addition, we are running a travel clinic for international travelers where we can treat tropical diseases with orphan drugs.

For research we are involved in various clinical trials such as chemotherapy for lung cancer, antimicrobial drugs, GM-CSF therapy for pulmonary alveolar proteinosis. Recently we have evaluated the clinical significance of transbronchial biopsy using Endobronchial Ultrasonography (EBUS) with a guide sheath. We are also investigating the pathogenesis of anti-GM-CSF antibody negative primary pulmonary alveolar proteinosis and familial pulmonary fibrosis.

For training and education, in addition to postgraduate training programs for resident physicians



Infectious disease conference

and for infectious disease and respiratory disease specialists, we are taking a part in education of undergraduate medical students by providing a number of lectures on infectious diseases and respiratory diseases and by bed-side teaching. Since April 2006, we have been organizing a clinical case conference for tropical diseases using English as a part of Master of Tropical Medicine course, Graduate School of Biomedical Sciences. Furthermore to accumulate our knowledge and experience with clinical tropical medicine, staff doctors and resident doctors are regularly dispatched for a long-term to San Lazao Hospital, the Phillipines and the infectious disease ward in Bac Mai Hospital, Vietnam.

#### Clinic at the University Hospital

mine at the emitersity in	opical
Professor	Koya Ariyoshi
Associate Professor	Konosuke Morimoto
Senior Assistant Professor	Yoshiko Tsuchihashi
Assistant Professor	Akitsugu Furumoto
Assistant Professor	Masayuki Ishida
Research Fellow	Mayumi Terada
Research Fellow	Takeshi Tanaka
Research Fellow	Kei Matsuki
Research Fellow	Yoko Tsumori
Research Fellow	Tomoko Ishifuji
Research Fellow	Maiko Kojiro
Resident Physician	Hiroyuki Ito
Resident Physician	Satoshi Kakiuchi
Resident Physician	Hiroshi Nakaoka
Assistant Professor	Shoko Honda
Assistant	Ayako Kitamura



Transbronchial Biopsy Using Endobronchial Ultrasonography With a Guide Sheath

# **Department of Immunogenetics**

This department is focusing on the pathogenic genetic factors of the host and the parasite in the most important tropical infectious diseases by using immunology and genetics.

#### Research activities:

To clarify the molecular mechanisms in the protective and/ or pathogenic host response to human pathogens such as Dengue Virus, TB, Malaria, Trypanosoma cruzi, Schistosoma, and Filaria, the following research projects are going on in our laboratory.

#### 1. Malaria

- 1) Genetic susceptibility to severe forms of malaria (cerebral malaria, severe anemia) is analyzed by case-control study in South East Asia, South Pacific and West Africa.
- 2) Malaria vaccine development using the immunological characteristics of resistant persons living in the endemic area in Asia and West Africa.

#### 2. Schistosomiasis

- 1) Immunological regulation of the pathogenic anti egg response in the resistant and susceptible persons, to post-schistosomal liver fibrosis in China and Philippines.
- 2) Miniature pig schistosomiasis as a human model.
- Vaccine development for schitosomiasis japonica and masoria using schistosomula antigens.
- 4) Production of the new diagnostic Kit for active infection.

#### 3. Chagas disease

- 1) Genetic susceptibility to different clinical types of chronia Chagas disease, namely, indeterminate, cardiac, and digestive forms, is analyzed by case control study in Bolivia where Chagas disease is still highly endemic.
- 2) Genetic analysis of Trypanosomes in Latia Americas by using local isolates and molecular biology.

#### **Collaborations:**

The research here is performed based on the well

Department of immunogenetics

arranged collaborative projects with the following facilities.

- Malaria: Thammasat University (Thailand), Noguchi Memorial Medical Research Institute (Ghana), Institute of Medical Research (Malaysia), Karolinska Institute (Sweden), Dokkyo University (Tochigi), WHO/TDR (Geneva Switzerland)
- Schistosmiasis: Jiangxi Provincial Institute of Parasitic Diseases (China), Jiangsu Provincial Institute of Parasitic Disease(China), Univ. Philippines and RITM (Manila, Philippines), Tokyo Medical Dental Univ. (Tokyo)
- 3. Chagas Disease: Center of Tropical Medicine and Hospital Japones (Bolivia), IICS University of Asuncion (Paraguay)

#### 4. Dengu virus

1) Pathogenesis of the DHF (Dengue Hemorragic Fever)

Host factors will be detected by the Populational genetic analysis of the patients with DHF and non DHF.

#### **Staffs**

Professor Kenji Hirayama Michio Yasunami Professor Associate Professor Nobu Ohwatari Senior Assistant Professor (Project) Mihoko Kikuchi Assistant Professor Nguyen Huy Tien Hiroki Shibata Assistant Professor Assistant Professor Shuaibu Mohammed Nasir Assistant Junko Hayashima Maki Jvoshita Assistant COE Technician Kaori Kamei Assistant Makiko Okamoto Graduate Student Akiko Takaki Graduate Student (Recseach Fellow) Akiko Yamazaki Graduate Student Helegbe Gideon Kofi **Graduate Student** Tran Thi Ngoc Ha **Graduate Student** Del Puerto rodas Ramona Florencia Daniel Boamah Graduate Student Graduate Student (COE researcher) Cherif Mahamoud Sama Graduate Student (COE researcher) Lam Quoc Bao Graduate Student Omar Ahamed Din Hassan Graduate Student Mbanefo Evaristus Chibunna Graduate Student (Visiting researcher) Edelwisa Segubre Mercado



**Experiment scenery** 

# **Department of Preventive Medicine and AIDS Research**

This department was newly added to the institute in 1978 as a research division open to visiting professors from other universities and institutes. This department is organized by an assistant professor. We are studing several retroviruses, human immunodeficiency virus (HIV), murine leukemia virus (MLV), and other mammalian retroviruses. HIV is an etiological agent of acquired immunodeficiency syndrome. MLV has been isolated from human patients with prostate cancer or chronic fatigue syndrome.

#### Study on the mechanism of viral entry into host cells by retroviruses

Human immunodeficiency virus (HIV) is known to be a causative agent for acquired immunodeficiency syndrome. After the HIV recognizes CD4 and chemokine receptor, for example CXCR4, it enters into target cells mediated fusion between virus envelope and cell membrane. Murine leukemia viruses are divided into four roups according to the infection receptors (ecotropic, amphotropic, polytropic, and xenotropic), and enter into host cells by same manner. It is most likely that the environment around the receptors influences the infection efficiency. We have reported that glycosylation of the infection receptors on host cells inhibits the retrovirus infections, and localization of the infection receptors in raft microdomains enriched with choresterol and glycolipids are important for the

Laboratory for biochemical research

infections.

On the other hand, there are some evidences showing that actin-dependent clustering of the infection receptors is involved in the retrovirus infection. The receptors, however, do not directly associate with actin. We have reported that ezrin, radixin, moesin proteins expressed in host cells function as the linker molecules between the infection receptors and actin cytoskeleton.

#### Study on murine leukemia virus

It has been recently reported that murine leukemia virus (MLV) was isolated from human patients with prostate cancer or chronic fatigue syndrome, suggesting that the MLV is a novel zoonosis infectious agent between human and mouse. We have shown that the infection receptors of MLV have been evolved to become resistant against the MLV infection in several rodent cells. Additionally, we have reported that the MLV infection occurs through acidic endosomes and requires host cathepsin proteases.

Visiting Professor Visiting Associate Professor Hironori Sato Assistant Professor Assistant

Naoki Yamamoto Yoshinao Kubo Naomi Yamatani



Laboratory for biochemical research

# Department of Eco-epidemiology

April 2008, the Research Center for Tropical Infectious Diseases was reorganized and transformed into four groups i.e. two departments in the Research Field of Environmental Medicine, Tropical Medicine Museum and the Kenya station of Overseas Research Stations.

Eco-epidemiology department is one of the new two departments in the Research Field of Environmental Medicine.

However, the staffs mainly work for the Kenya Research station of Overseas Research Stations and for the Tropical Medicine Museum.

Professor Masaaki Shimada (Kenya Station)

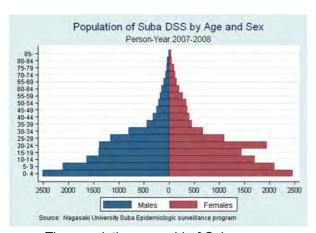
Professor Satoshi Kaneko

Professor Yoshio Ichinose (Kenya Station)

Assistant Professor Kensuke Goto
Postdoctoral Fellow Michiko Ogino
COE Research Fellow Yoshito Fujii
COE Technician Emi Nakayama

The concept of eco-epidemiology is based on the view of recognizing tropical diseases as a system of infection. The aim of our research is to understand the process of interaction between microorganisms, vectors and human beings in the system.

Human beings and vectors, so-called hosts as a niche of pathogens, exist not statically but dynami-



The population pyramid of Suba area.

cally in time and space. In addition, there is an infinite diversity in the characteristics of hosts. We study how microorganism survive, maintain, proliferate, diminish, disappear and emerge through the niches.

The ultimate purpose of the department is to form a theory for a better understanding of the interrelationship between hosts and pathogen and its consequences, diseases.



Prof. Ichinose, collecting stool samples from cholera patients in an isolation ward.



Prof. Kaneko, checking field data with James Kopiyo.



Group photo at a symposium held 4th December 2009 at KEMRI.

# Department of International Health

Department of International Health has started its activities since 2008, following the internal reform of Institute of Tropical Medicine. Department of International Health has its basis on Research Center for Tropical Infectious Diseases (RECTID) of Institute of Tropical Medicine established in 2001, Information and Reference Center in 1997, and Reference Center in 1994.

It says that RECTID, a precursor of our department, had following three activities; 1) developing the museum of tropical medicine, 2) collecting and disseminating information on tropical infectious diseases and 3) promoting joint research projects and doing epidemiological studies. Out of which, Department of International Health takes over research activities and adds to its mandate an international collaboration as a social responsibility anew.

Thus, Department of International Health, as a newly established department, has two pillars, e.g. research and social responsibility.

Research was composed of three units; 1) research on infectious diseases in ecosystem, 2) research on the environment including climate change and Asian dust related to health, 3) research on biological evolution of microorganisms from the adaptation or fitness view point. The umbrella concept or key word linking above three research units is to reconstruct infectious diseases "temporally" and "spatially" alike. Infection is the biological 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.

Another pillar 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.

Our department raises following three activities as international contribution; advocacy on international health at national and international level, health promotion activities and empowerment at the community/ grassroots' level and emergency relief.

What our department thinks of important in those activities is to make solidarity in order to improve people's health and contribute to people's sustainable development. It is our department's goal.

Professor Associate Professor Assistant Professor Assistant Professor Assistant Professor Assistant Professor Visiting Researcher Visiting Researcher Visiting Researcher Visiting Researcher Assistant Assistant Assistant Assistant Graduate Student Graduate Student Graduate Student **Graduate Student Graduate Student Graduate Student Graduate Student Graduate Student Graduate Student** Graduate Student

Taro Yamamoto Junko Okumura Toshihiko Sunahara Masahiro Hashizume Takeshi Yoda Katsuyuki Equchi Guoxi Cai Liang Qin Eiko Kobori Taizou Wada Hidefumi Fujii Zhuo Zhang Satsuki Shiraishi Akiko Hayashi Osuke Komazawa Keiko Akahane Kounnavong Sengchanh Mika Ohki Md. Manirul Islam Ubydul Haque Katsura Igai Kenji Mizumoto Vu Hai Ha

Etsuko Hatagishi



# Department of Vector Ecology & Environment

Our research interests include anything from ecology to molecular biology of medically important arthropods, particularly mosquitoes that transmit diseases such as malaria and dengue. We are also interested in their relationships with environmental factors and development of environmentally friendly vector control strategies.

#### 1. Dengue vectors

As dengue vectors are extending their geographic distribution, the spread of the disease is being concerned. It has been suspected that the expansion of vector distribution is due to environmental factors such as climate change. We are currently mapping their distributions in Vietnam and Kenya, and examining the relationship with environmental factors. In NyaTrang city, southeast Vietnam, we are examining the key environmental factors that contribute to the spread of the disease.

#### 2. Malaria vectors

Main malaria vectors belong to a group of sibling species, and members within a group are morphologically indistinguishable. We are examining ecological and physiological differences among the members within the Anopheles gambiae complex group and the Anopheles funestus complex group. We are also investigating their geographic distributions in East Africa. This extensive field survey was designed to understand the effects of

climate and the Great Rift Valley on their distributions and evolution.

#### 3. Vector control measures

The coverage of insecticide treated bed nets has considerably increased in Africa. We are investigating whether local residents properly use and maintain bed nets, and how long bed nets last. We are also investigating the effects of bed nets on the species composition of vectors and their behavior, and monitoring their insecticide resistance in Kenya and Malawi.

#### 4. Detection of virus in mosquitoes

We collaborate with National Institute of Infectious Diseases in Japan and National Institute of Hygiene and Epidemiology in Vietnam to detect new viruses from a variety of mosquito species.

Professor	Noboru Minakawa
Associate Professor	Hitoshi Kawada
Assistant Professor	Yukiko Higa
Assistant Professor	Takashi Tsunoda
Assistant Professor	Kyoko Futami
Research Fellow	Yoshihide Maekawa
Research Fellow	Ataru Tsuzuki
COE Research Fellow	Hu Jinping
Assistant	Emiko Kawashima
Assistant	Chiaki Tsurukawa
Assistant	Naoko Mori
Assistant	Junko Sakemoto
Graduate Student	Endan Pujiyati
Graduate Student	Koji Yamada
Graduate Student	Hanako Iwashita





# **Center for Infectious Disease Research in Asia and Africa**

#### **OKenya Research Station**

#### Outline of the program

The Institute of Tropical Medicine (ITM) has received a government grant for the promotion of research on tropical diseases and emerging and reemerging infectious diseases. With this special grant of money, ITM established a research station in Nairobi and research field in Suba area in South Nyanza, Kenya (October 2005 - March 2010). ITM continuously received a government grant for tropical disease research and clinico-epidemiological research (April 2010 - March 2016). The unique feature of this research program is long-term, extensive, and multidisciplinary studies based on Japan-Kenya collaboration. The program provides training for young researchers both Japanese and Kenyan, and in collaboration with JICA, it contributes to the disease prevention and treatment of tropical and emerging infectious diseases in the tropics with the fruits of its research.

#### Progress of the program

#### 1. Research station in Kenya

The Kenya Research Station was established to facilitate bio-medical and epidemiological studies in tropical diseases. A P3 laboratory in Nairobi and Demographic Surveillance System in Suba area was established. A Laboratory in KEMRI Production Department for virus research has been established in 2009 and a new research field on Schistosomiasis in Kwale was established in July, 2010.

#### 2. Dispatch of Japanese researchers

Five professors, an associate professor, a JSPS-JICA expert, two research associates, two postdoctoral fellows, and administrative staff members in the Kenya Research Station are dispatched.



Main office of Kenya Research Station (made in cargo containers)

# 3. Study areas for the long-term and extensive research work

A Demographic Surveillance System (DSS) and a Mosquito Surveillance System (MSS) are in operation in the Suba area of Western Kenya. A joint project with JICA (JICA Partnership Program) started in 2009 in Suba. A DSS started of its operation in Kwale area on the Coast in July, 2010. Grant Assistance for Grassroots Projects (GGP) of Embassy of Japan also started in Suba area in 2010.

#### 4. Studies in infectious tropical diseases

Based on the DSS in Suba, research on malaria was launched in 2006. Study on diarrheal diseases and septicemia started in Kiambu district in 2008 and 2010. Study on arbovirus and parasitic diseases started in 2008. In Kwale, research on Schistosomiasis was launched July 2010. Study on diarrheal disease in Suba will start in 2010.

#### 5. Training program

Under the patronage of JICA and MEXT, Kenyan researchers and doctors have been given opportunities to visit ITM and were trained in research on tropical medicine. Professors of ITM served as advisers in the JICA-sponsored International Parasite Control which took place in Kenya.

#### **Program Staff**

Leader and Professor Yoshio Ichinose (Kenya Station)
Professor Masaaki Shimada (Kenya Station)

Professor Noboru Minakawa
Professor Sinjiro Hamano
Professor Satoshi Kaneko
Associate Professor Hitoshi Kawada
Assistant Professor Toru Kubo
Assistant Professor Kyoko Futami
Postdoctoral Fellow Michiko Ogino
Research Fellow Yoshihide Maekawa

COE Research Fellow Hu Jinping

Administrative Staff Haruki Kazama (Kenya Station)
Administrative Staff Yukie Saito (Kenya Station)

JICA Expert Singo Inoue (Kenya Station)

(Assistant Professor)



Staff members

# **Center for Infectious Disease Research in Asia and Africa**

#### **OVietnam Research Station**

#### Outline of the research center

The institute of Tropical Medicine (NEKKEN) and National Institute of Hygiene and Epidemiology, Vietnam (NIHE) have jointly been managing a fiveyear project, entitled "Collaborative Study on Emerging and Re-emerging Infectious Diseases in Vietnam" since 2005, and achieved the objective of the project at a satisfactory level. Meanwhile, agenda of the next phase five-year project was underlined, which is, clarifying the factors and their mechanisms in causation of emerging and re-emerging infectious diseases. In the second phase project, "Japan Initiative for Global Research Network on Infectious Diseases (J-GRID)", we will develop researches under four research groups (diarrhoea, vector-borne infectious diseases, clinical research, and zoonosis) in the similar framework of the collaborative studies by NEKKEN and NIHE to attain the objective of the project. We wish results from researches in the project render help to the activities regarding public health promotion and medical care.

#### Research activities

The objectives of the entire project are to clarify the ecology of pathogens in nature and in human society, to clarify the pathogenic mechanism of human diseases, and to develop an intervention-based method to inhibit the spread of infectious diseases. Four research groups will conduct their researches pursuing their research objectives. Research agenda are as follows:

**Diarrhoea research group**: 1) A molecular epidemiological study on kinetics of enteropathogens after rotavirus vaccine intervention, 2) A molecular epidemiological study of Vibrio cholerae in ecosystem in Vietnam, and 3) Human animal interface in causation of diarrhoea in Vietnam.

Vector-Borne Infectious Diseases Research Group:
1) Study on biological properties, virulence and ecological significance of dengue viral quasispecies in mosquito vectors and humans, 2) A survey of Japanese encephalitis virus migration, 3) A study of the



Staff of Vietnam Research Station

influence of arbovirus on seasonal encephalitis of unknown origin, 4) A survey of climate change, mosquito vectors, and virus infection, 5) A study of mosquito vectors, pathogenic mechanism of dengue fever, and anti-infection measures.

Clinical Research Group: 1) Pediatric acute respiratory infection cohort research study, 2) A birth cohort study, 3) An immunogenetical analysis of severe dengue fever at Choray Hospital, 4) Establishment of a clinical and epidemiological research data collection system for analysis of the fever of unknown origin

**Zoonosis Research Group**: 1) A viral epidemiological study of bat-borne infectious diseases, 2) A molecular epidemiological study of rabies, 3) An epidemiological study of hantavirus, 4) Development of human monoclonal antibody with neutralizing activity against avian influenza (H5N1) strain, 5) An epidemiological study of avian influenza.

# NIHE-Nagasaki University Friendship Laboratory (NNFL) staff

Professor
Professor
Assistant Professor
Assistant Professor
Assistant Professor
Assistant Professor
Assistant Professor
Administrative Staff
Research Assistant

Tetsu Yamashiro
Futoshi Hasebe
Takashi Tsunoda
Hiroshi Yoshino
Gen-ichiro Uechi
Kozue Hotta
Jiro Hirau
Dang Thi Dinh
Le Thi Thuyen
Ngo Khanh Phuong
Nguyen Thi Yen
Quach Thi Thu Huong
Ung Thi Hong Trang
Bui Thu Tra



Dr. Uechi is providing a basic technique to perform PCR to a Vietnamese staff



A surveillance for mosquito which potentially transmit dengue viruses

# **Tropical Medicine Museum**

Museum of Tropical Medicine was preceded by the Tropical Medicine Reference Centre, which was established in 1974 and was reorganized in 1997 as Tropical Medicine Reference and Information Center. In 2001, it was renamed as Research Center Tropical Infectious Diseases (RECTID) and in 2008 it was established as an auxiliary institution. The institution performs the following 2 functions.

The institute primarily functions as a museum and resource center for tropical disease. Currently, on the 1st floor of the Institute of Tropical Medicine Nagasaki University, there is a general section providing information on tropical diseases, parasites/ bacteria/viruses/poisonous insects and specimen of dangerous animals, valuable books, and displays images of the data. Moreover, it has an audio- visual room accommodating a few numbers of people. Furthermore, a system is being developed for using this collection of resources to strengthen public science and risk communication with thousand points relating to the history and philosophy of tropical medicines and infection symptoms. In the near future we would like to expand the exhibition room to the museum of tropical medicine and can be used as an educational resource for society and educators and provide tropical disease related research and successful results for the public. In addition, we displayed Africa's Nature, Development, and People, in March 2009, as part of the Ueno Yama Decade of Information series of National Museum of Nature and Science, Tokyo.

It also functions as an information center for the



dispatch, collection, organization, and analysis of information on tropical medicine. This has become an essential component of the daily research activities related to tropical medicine. Due to infrastructure rearrangement in 2007, network tools were updated with technological innovation and long lasting safety; thus responding to every need of the users. We also serviced various databases, using a research evaluation system and a database of the tropical medicine museum. Moreover, we are trying to provide a similar environment to research universities overseas with VPN by including video conferencing system to promote international conferences and e-learning plans.

Head and Professor Noboru Minakawa
Professor Masahiro Horio
Assistant Kazuo Araki
Assistant Kiyomi Suda
Assistant Akiko Akita



# **Central Laboratory**

#### **OLaboratory of Molecular Biology**

Investigation of the interaction between microbial pathogens, vectors and hosts at molecular or gene levels is important for the better understanding of pathogenesis of various infectious diseases. Molecular Biology Laboratory has been equipped with 16- and 48-capillary sequencer for high-throughput and high-resolution genetic analysis of pathogens. vectors and hosts. In addition to general laboratory facilities such as, pure water supply, ultracentrifuge, lyophilizer, sample storage in liquid nitrogen, biosafety cabinet, autoclave, dark room and cold room, the laboratory is also equipped with several special analyzers such as laser confocal microscope, twodimensional HPLC-based proteome analysis system, flowcytometer, digital cell sorter, Luminex bead-array system, Pyrosequencer, fluorescenceand luminescence-multilabel counter, fluorescenceand luminescence-imager, mass spectrometrybased genotyping system to meet a variety of demands of researches of the institute as well as those of visiting investigators.

### **OLaboratory of Pathology**

Main purpose of our research is fundamentally pathological investigation of tropical diseases, mainly infectious diseases, focused on oncogenic microbes, and establishes the basis of their treatment and prevention. Although many investigators have proposed oncogenesis due to inflammation associated cancer development, the mechanisms underlying the relationship between chronic inflammation and cancer still remain unresolved. Therefore, our research focuses on the potential role of oncogenic microbes in the development of cancers, highlighting the recent advances in the understanding of the molecular mechanisms.

The proportion of total cancer deaths attributable to infectious agents is estimated to be 20% to 25% in developing countries and 7% to 10% in industrialized countries. A causal relationship between chronic inflammation and cancer is widely accepted. Specifically, there is a strong association

between tumor viruses and the development of human cancers. The mechanisms of oncogenesis associated with infection and inflammation have not been elucidated. However, many oncogenic mechanisms have been proposed for infection and inflammation. Activation of NF-  $\kappa$  B is also involved cancer development and progression. Therefore, our research focuses on the molecular players during the development from chronic inflammation to cancer.

### **Electron Microscope Room**

Electron microscopy has been applied to the inspection of the ultrastructure of most microbial pathogens including viral, protozoal and bacterial speciesas well as to the detailed morphological analysis of host-pathogen interactions by means of immuno-histochemical procedures and other moderntechniques. The laboratory is equipped with transmission electron microscope (from JEOL), scanning electron microscope (from JEOL), ultramicrotome (fromReichert), vacuum coater, critical point dryer system, and osmium plasma coater in addition to general laboratory facilities for a wide range application of electron microscopy, contributing to various research projects in the institute and collaborations with the other researchers.

Head and Professor Kouichi Morita
Assistant Professor Masachika Senba
Research Associate Akitoyo Ichinose
Assistant Kanae Tanaka



Lab for Genetic Analysis

### **Animal Research Center for Tropical Infections**

The center makes it the principal aim to ensure the safety of animal experiments which are dealt with the pathogenic microorganisms and to build up the continuous production of experimental animals, microorganisms and parasites. The building consists of seven breeding rooms for experimental animals, three laboratories, one breeding room for snails and insects, and a P3-level biohazard laboratory.

The temperature of all the rooms is kept 25C all the year round. The air pressure is kept always negative to avoid outflow from inside. Since the building has the most thorough ventilation through HEPA filters, any microbes cannot leak out to outside of the building. The used cages are reused after autoclave-sterilization, and used water is drained off after chlorination. The laboratory animals bred in the center are mice, rats, hamsters, gerbils, rabbits, snails and mosquitoes. The number of users in 2009 was around 7,000.

The breeding and experiments are done according to Nagasaki University Animal Experiment Regulations.

Head and Professor Shinjiro Hamano
Research Associate Tetsuo Yanagi
Assistant Junko Kawashima



a laboratory in ARCTI

### Administration

Toshihiro Furukawa, Director Hiroaki Suetsugu, Expert Staff

#### **General Affairs Unit**

Makoto Matsuo, Head Risa Yamashita, Sub-Head Naomi Ota, Staff Miyuki Yamashita, Assistant Staff Eiko Sanefuji, Assistant Staff

#### Accounting and Facilities Management Unit

Takenobu Hayashida, Head
Tomohiro Ito, Sub-Head
Yoko Oya, Staff
Junko Nagata, Assistant Staff
Yumiko Matsumoto, Assistant Staff
Asuka Matsuo, Assistant Staff
Risa Tatsuhara, Assistant Staff
Kozue Tsujita, Assistant Staff

#### **Overseas Research Station Unit**

Kenta Sasada, Head
Fumiko Hashiguchi, Sub-Head
Saeko Tano, Staff
Haruki Kazama, Staff
Yukie Saito, Staff
Idumi Hasegawa, Assistant Staff

# **Number of Staff**

(as of May, 2010)

Divisions	Professor	Associate Professor	Lecturer	Assistant Professor	Research Associate	Sub total	Others	Total
Enrollment	9 (5)	4 (1)	2	15 (17)	3	33 (22)	10 (5)	43 (27)

 $<sup>\</sup>frak{\%}$  ( ) number of fixed-term staff

# Accounting

#### Revenue (in 2009)

Divisions	Amount (in thousands)
Tuition and Admission Fees	1,889
Others	250
Total	2,139

#### Expenditure (in 2009)

Divisions	Amount (in thousands)
Personnel expenses	504,070
the cost of equipment	372,735
Total	876,805

# Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology

(in 2010)

Type of Research		Scientific Research on Innovative Areas	Scientific Research (A)	Scientific Research (B)	Scientific Research (B)	Scientific Research (C)	Challenging Exploratory Research	Young Scientists (B)	Total
Number of Grants	2	1	1	7	3	6	2	6	28
Amount (in thousands)	9,800	3,120	15,210	38,480	22,880	8,970	1,400	10,400	110,260

Facilities & Administrative costs included

# Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare

(in 2010)

Type of Research	Global Health Issue	Emerging and Reemerging Infectious Diseases	AIDS Control	Clinical Cancer	Total
Number of Grants	2	4	3	1	10
Amount (in thousands)	14,889	9,900	5,600	1,500	31,889

# Subsidy

(in 2009)

Type of Research	Grant-in-Aid for Forming Research Locations etc (Global COE)	National Bio-resource Project (NBRP)	Special Coordination Funds for Promoting Science and Technology of the Ministry of Education, Culture, Sports, Science and Technology
Amount (in thousands)	318,929	3,800	27,858

Facilities & Administrative costs included

# **External Funding**

(in 2009)

Divisions	Joint Research with Private Sectors	Commissioned Research	Commissioned Project	Endowments
Number of Sources	2	8	7	26
Amount (in thousands)	61,950	269,580	168,932	23,409

Facilities & Administrative costs included

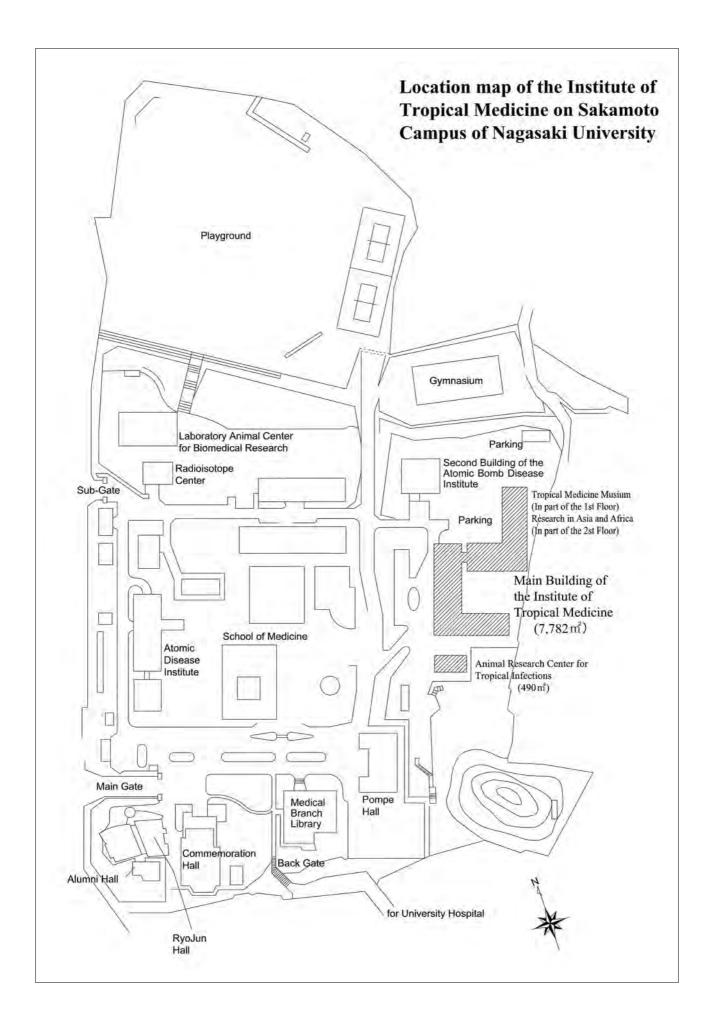
# Agreement of Educational, Scientific and Scholarly Exchange

#### Overseas

Name of organization of partner countries	Concluded date
Chiang Mai University (Thailand)	February, 1988
Mahidol University (Thailand)	November, 1999
University of the Philippines Diliman (Philippines)	April, 2001
National Institute of Hygiene and Epidemiology (Vietnam)	June, 2001
Airlangga University (Indonesia)	January, 2004
St. Luke's Medical Center (Philippines)	February, 2004
San Lazaro Hospital Medical Center (Philippines)	August, 2004
Kenya Medical Research Institute (Kenya)	November, 2004
Thammasat University (Thailand)	March, 2006
Defence Research and Development Establishment (India)	January, 2010

#### **O**Domestic

Name of organization of partner	Concluded date
The Research Institute of Tuberculosis Japan Anti-Tuberculosis Association	March, 2009



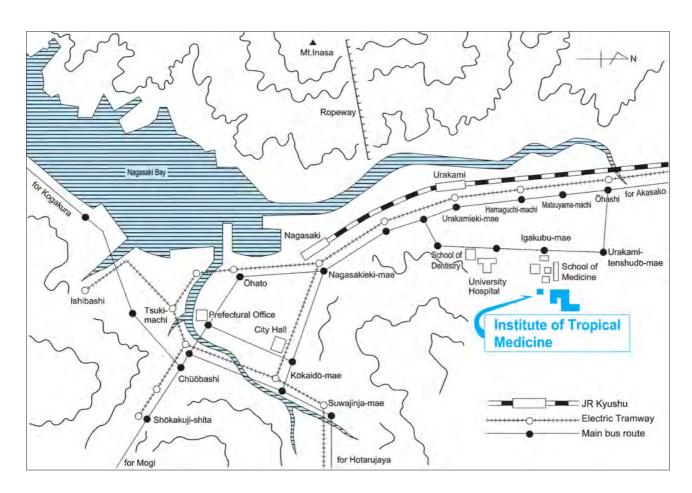
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Department	t of Preventive Medicine and AIDS Research										
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	Electron Microscope Room ······	7	8 5	9	8	1	9 –	- 7	8	5 9	)
	Information				8	1	9 –	- 7	8	5 7	7

# Location map of the Institute of Tropical Medicine, Nagasaki University in Nagasaki City



#### How to get the Institute

OFrom JR Nagasaki Station

► Electric Tramway "Nagasaki Station" → (bound for Akasako) → "Hamaguchi-machi"

→ about 10-minute walk

Nagasaki Bus "Nagasaki Station" → (No.8 bound for Shimoohashi via School of

Medicine) → "School of Medicine"

OFrom JR Urakami Station

► Electric Tramway "Urakami Station" → (bound for Akasako) → "Hamaguchi-machi" →

about 10-minute walk

OFrom Nagasaki Airport

► Kenei Bus "Nagasaki Airport No.4 Bus Stop" → (bound for Nagasaki City via

Showa-machi and Urakami) → "Urakami Station" → refer to "From JR

Urakami Station" above

#### Location

1-12-4 Sakamoto Nagasaki 852-8523 URL http://www.tm.nagasaki-u.ac.jp

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