

Global COE Program
Establishment of
International Collaboration Centers
for Zoonosis Control
Hokkaido University

Background and Objectives

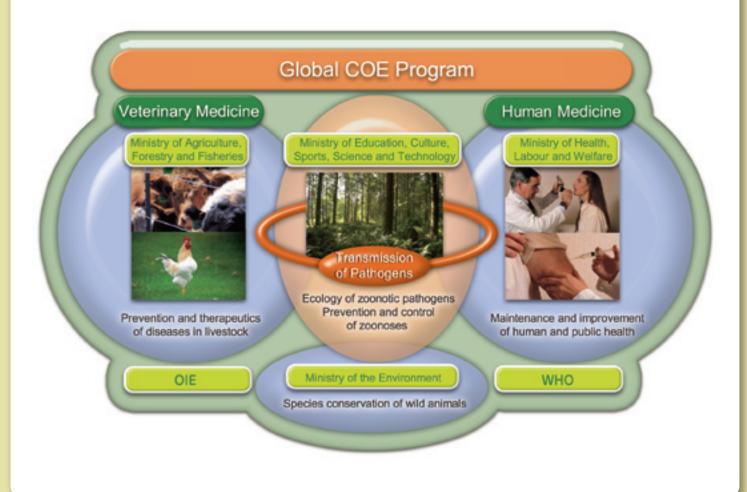
Emerging and reemerging infectious diseases, such as influenza, SARS, Ebola hemorrhagic fever, West Nile fever, prion diseases, tuberculosis and rabies, have recently been appearing with high frequency worldwide, and are becoming a major concern to public health. All of these diseases are zoonoses caused by agents that were originally harmless in their wild natural host animals and were occasionally transmitted to other animal species, including humans, causing infectious diseases. Changes in the global environment and human behavior contribute to the emergence of new diseases by changing transmission dynamics and bringing people into closer and more frequent contact with pathogens. In addition, the emergence of multidrug-resistant bacterial infections is also a public health concern.

However, there was previously no research organization or network specializing in the control of zoonoses, and we also face a lack of human resources for the control of such diseases. One of the reasons for this is that research and education in medicine are targeted at maintaining and improving human and public health, while those in veterinary medicine are aimed at the prevention of infectious diseases and the clinical treatment of livestock and pets. Administrative barriers (i.e., medical and veterinary activities under the direction of the Ministry of Health, Labour and Welfare, and the Ministry of Agriculture, Forestry and Fisheries, respectively) have also been a hindrance. Thus, there is no research or educational/administrative basis for the control of zoonoses, since the issue falls between the two sciences of human and veterinary medicine. Zoonosis outbreaks often occur in the current worldwide

situation, causing irrevocable damage to human lives due to the lack of clarity regarding the responsibility for zoonosis control measures.

In our previous 21st COE program entitled Program of Excellence for Zoonosis Control, we investigated the ecology and transmission routes of zoonotic pathogens, established national and international networks, developed novel methods for the diagnosis, prevention and therapy of zoonoses, and provided training courses for personnel who conduct control management at the sites of disease outbreaks. To further these progressive activities, Hokkaido University established the Research Center for Zoonosis Control on April 1, 2005. The Program of Excellence for Zoonosis Control and the Research Center for Zoonosis Control have contributed to international education and scientific achievements for the control of zoonoses, and also act as a global surveillance center and influenza reference laboratories for the World Health Organization (WHO), the Food and Agricultural Organization (FAO) and the Office International des Epizooties (OIE). We have also conducted zoonosis control training courses for researchers from around the world.

On the basis of these achievements and the international collaboration research network established, we propose a new organization "the International Collaboration Centers for Zoonosis Control" in this global COE program. We will foster zoonosis control doctors who are responsible for the control of zoonoses worldwide.



Outline of Activities

Under this program, we will work to clarify the perpetuation mechanisms and transmission routes of zoonotic pathogens in nature, the molecular mechanisms of host range and the pathogenesis of zoonotic diseases, establish prophylactic and therapeutic strategies, and participate in an exhaustive search for potential zoonotic pathogens, with the aid of the international collaboration research network. Through our research and educational activities, we will forster zoonosis control doctors who will play pivotal roles in the control of zoonoses at the epicenters of outbreaks and make major contributions to international and domestic activities for disease control.

Organization

The program will be mainly implemented by four subgroups:

Cultivation of Human Resource Group

This group will provide active support for the development of research ability and the international activities of post-graduate and post-doctoral students. It will also support the development and implementation of career paths for students and trainees who have acquired outstanding research skills.

Epidemiological Research Group

This group will investigate the perpetuation mechanisms, distribution, host specificity and transmission routes of pathogens in nature, as well as performing an exhaustive search for novel microorganisms that may potentially cause zoonoses in the future. In addition, strategies for the prediction, prevention and control of endemic infectious diseases will also be developed via bioinformatic approaches.

Immunological and Pathobiological Research Group

This group will examine the mechanisms underlying pathogenicity, host range and immune responses. The information obtained will be used to advance the establishment of prophylactic and therapeutic strategies.

Diagnostic and Therapeutic Research Group

This group will develop novel strategies for diagnostic, therapeutic and prophylactic methods, animal models for zoonosis research, and technologies for the isolation and identification of pathogens.



Educational Activities

i) Support for international activities and development of a sense of responsibility for worldwide disease control for Ph.D. course students and young researchers

This program will support the overseas activities of students in Ph.D. course and young researchers at Hokkaido University who want to learn practical epidemiology and need to develop a sense of responsibility for worldwide disease control. We will utilize the overseas institutions established by our previous 21st COE program and the Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases, supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). Lectures and practical training are to be annually provided by experts on infection control. We will encourage young researchers to organize international symposia. Specialists in risk management will also be educated with the aid of the MEXT International Training Program, in which we will send Ph.D. candidates and young researchers to overseas laboratories that operate Biosafety Level 4 facilities.

ii) Training of zoonosis control doctors

The educational program is designed to train Ph.D. candidates, graduates and young researchers from relevant domestic facilities and overseas collaborative establishments, thus forstering zoonosis control doctors who will be responsible for the control of zoonoses worldwide.

iii) Enhancement of education for students from abroad

In collaboration with the International Priority Graduate Programs scholarship scheme adopted by MEXT in 2007, the process of the Ph.D. course for students from abroad will be improved. Masters course education specializing in infectious diseases will be established during this COE program. Through the training courses described above, we will develop human resources who will participate in the international collaboration research network and play a vital role in the control of zoonoses in their own countries.

iv) Encouragement of Ph.D. candidates to design original research projects

Research plans will be proposed by Ph.D. candidates. Students whose plans are adopted by the scientific committee consisting of faculty members on the COE program will be promoted to research assistants, and will receive financial support under the program.

v) Education for young researchers and technicians in overseas institutions

In our previous 21st COE program, we conducted zoonosis control training courses for researchers and technicians from other countries. In this global COE program, we will conduct an advanced training course for zoonosis control that will provide lectures and practical training with higher levels of knowledge and technology than the previous ones.

Research Activities

Epidemiological Research Group

Perpetuation mechanisms of pathogens in nature

Global surveillance to identify natural host animals and transmission routes of pathogens, as well as an extensive search for unknown potential zoonotic pathogens (i.e., candidate microorganisms that may emerge as new pathogens for humans and animals), will be conducted with the aid of the international collaboration research networks that have been established.

Bioinfomatic approach for the prediction and prevention of zonoses

By fusing bioscience and informatics, we will analyze masses of biological data sets to find causative factors for infections, and intend to establish strategies to predict and prevent the occurrence of zoonoses and their spread.

Immunological and Pathobiological Research Group

Host range and pathogenesis

The molecular bases of the mechanisms underlying host range and the pathogenesis of zoonotic infections caused by viruses, bacteria, protozoa, parasites and prions will be investigated.

Immune responses against infection

The mechanisms underlying the innate and aquired immune

responses induced upon infection with microorganisms will be clarified.

Diagnostic and Therapeutic Research Group

Prophylactic and therapeutic strategies

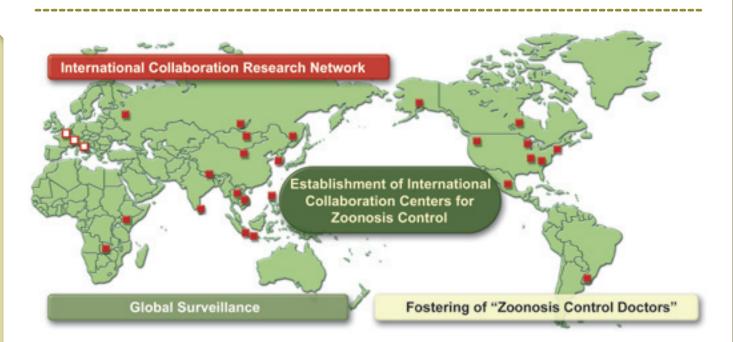
We intend to develop novel vaccination strategies, including immunogens, adjuvants and administration routes. Based on the information obtained from the research activities described above, novel prophylactic and therapeutic strategies will be developed.

Diagnostic methods

We will develop novel diagnostic methods, such as rapid and simple detection kits with high sensitivity and specificity to pathogens, which will be employed in field research and for bedside use.

Cultivation of Human Resource Group

All members of this group also belong to other research groups to carry out their own research activities.



Collaboration with International Organizations

World Health Organization (WHO), World Organization for Animal Health (OIE), Food and Agriculture Organization (FAO)

International Collaboration

Autonomous Metropolitan University, Mexico, Bogor Agricultural University, Indonesia, Centers for Disease Control and Prevention, USA, Department of Medical Research, Myanmar, Everest International Clinic and Research Center, Nepal, International Livestock Research Institute, Kenya, Lanzhou Veterinary Institute, China, Leonard Wood Memorial, The Philippines, National Institute of Animal Health, Thailand, National Institute of Health, Research Hospital, USA, Tribhuban University, Nepal, University of Peradeniya, Sri Lanka, University of the Republic, Uruguay, University of Wisconsin, USA, University of Zambia, Zambia, Yale University, USA. National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rocky Mountain Laboratories, USA

Program members



Professor, Department of Disease Control, School of Veterinary Medicine, Director, Research Center for Zoonosis Control, Director, OIE World Reference Laboratory, Hokkaido University Member of the Japan Academy

Program Leader

KIDA, Hiroshi, DVM, PhD, MJA

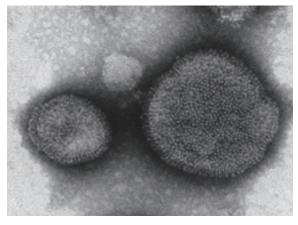
"Management of the Program, and Ecology of infectious agents for the prevention and control of zoonoses"

For the preparedness for and control of avian and human influenza, Prof. Hiroshi Kida has been devoted himself in elucidating molecular basis of the ecology and pathogenicity of influenza viruses in nature, birds, mammals including humans, and mechanisms of the emergence of pandemic influenza virus strains in poultry, domestic animals and humans. Japan Academy Prize was awarded to Prof. Hiroshi Kida for "Studies on Control of Influenza - Mechanism of Emergence of Pandemic Influenza Virus Strains in Poultry, Domestic Animals and Humans, and Molecular Basis of the Neutralization of Viral Infectivity with Antibodies-" in 2005. He was selected as a Member of the Japan Academy in 2007. In the present Program of Global Center of Excellence, he will continue to conduct global surveillance of avian and mammalian including human influenza, diagnosis, and training of researchers and technical officers in the

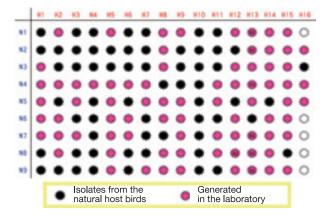
world as a member of WHO human/animal interface surveillance network and OIE/FAO World Reference Laboratory. In Japan, he will continue to direct the policy for the prevention and control of avian influenza as the Chairman of the Committee for the Control of Avian Diseases, the Ministry of Agriculture, Forestry and Fisheries.

He will establish a library of non-pathogenic avian influenza virus strains of 144 combinations of HA and NA subtypes and their genes for vaccine strain candidates and diagnostic use and open to supply for the world. Using virus strains of the library, he will develop effective vaccines for poultry and human use.

He will foster Zoonosis Control Doctors who will contribute to prevention and control of zoonoses in the world.



Electron micrograph of influenza A virus particles



Library of non-pathogenic influenza virus strains of 144 combinations of HA and NA subtypes

Cultivation of Human Resource Group

SUGIMOTO, Chihiro

Professor, Dept. of Education and Collaboration, Research Center for Zoonosis Control



"Cultivation of human resources for zoonosis control"

The development of human resources is one of the major objectives of this program. This group provides active support for the development of research ability and the international activities of post-graduate and post-doctoral students. We also support the development and implementation of career paths for students who have acquired outstanding research skills. All members of this group also belong to other research groups to carry out their own research activities.

"Research on arthropod-borne protozoan infections"

In order to seek control measures for infectious diseases caused by arthropod-borne protozoans and rickettsiae, analyses of their genomes, pathogenesis and ecology will be carried out. Research subjects include pathogens in the genera *Trypanosoma*, *Theileria* and *Ehrlichia* found in the African continent, as well as the vector ticks and tsetse flies that transmit them. In particular, gene databases of parasites and vectors will be developed and utilized to enable analysis of the triangular relationships between parasites, vectors and mammalian hosts.

KARIWA, Hiroaki

Associate Professor, Lab. of Public Health, Dept. of Environmental Veterinary Sciences, Graduate School of Veterinary Medicine



"Education and research in epidemiology of zoonoses"

In recent years, viral zoonoses including West Nile fever, tick-borne encephalitis and hantavirus infections have given rise to serious public health concerns both domestically and globally. To provide preventive measures against these zoonoses, new diagnostic tests will be developed. In addition, epidemiological surveys will be conducted to identify the endemic areas and reservoir animals involved. The genetic, antigenic and pathogenic characteristics to the viruses will be also analyzed.

AGUI, Takashi

Professor, Lab. of Laboratory Animal Science and Medicine, Dept. of Disease Control, Graduate School of Veterinary Medicine



"Education and research for establishment of animal models

Mx and Oas1b genes are expressed in an interferon-dependent manner when infected by orthomyxoviruses and flaviviruses, respectively, and have specific antiviral activity to each virus in the host cells. Our work includes analysis of the functional mechanisms of Mx and Oas1b against orthomyxovirus and flavivirus infection, respectively. We also study the structure and function of Mx and Oas1b in feral rodents, which may be carriers of these viruses in the field.

KATAKURA, Ken

Professor, Lab. of Parasitology, Dept. of Disease Control, Graduate School of Veterinary Medicine



"Education and research for control of parasitic diseases"

We continue to focus on canine parasitic diseases such as leishmaniasis, trypanosomiasis, babesiosis and echinococcosis. Our studies include the development and improvement of serological/molecular diagnostic tools for these diseases and the discovery and development of anti-parasitic compounds from natural medicinal plant sources. Research interests are also directed toward understanding the mechanisms of parasite transmission under natural environmental conditions and elucidation of the molecular/immunological mechanisms of parasite dissemination and persistence in the natural final host.

TAMASHIRO, Hidehiko

Professor, Dept. of Global Health and Epidemiology, Graduate School of Medicine



"Education and research in establishment of international networks"

As part of the development of the global network and human resources, we will conduct studies on rabies control strategies and on the epidemiology and control of leptospirosis in Sri Lanka, and will develop a network for research and training in these areas. In addition, we plan to continue expanding the roles and functions of the Hokudai International Research Center for Rabies Control at the University of Peradeniya and to further develop human resources, especially among young scientists in the Faculty of Medicine and the Faculty of Veterinary Medicine and Animal Science at the university.

ARIGA, Tadashi

Professor, Dept. of Pediatrics, Graduate School of Medicine



"Education and research in human healthcare"

We have studied the pathophysiological mechanisms of respiratory tract infection by emerging viruses such as human metapneumovirus (hMPV) and human bocavirus (HBoV). In particular, we focus on the study of (1) the development of diagnostic techniques for HBoV infection, (2) the analysis of the host immune system against HBoV infection, (3) the production of viral particles of HBoV using reverse genetic techniques, and (4) the development of an animal model of HBoV infection.

Epidemiological Research Group

TAKADA, Ayato

Professor, Dept. of Global Epidemiology, Research Center for Zoonosis Control



"Epidemiological research for zoonosis control"

The epidemiology research subgroup will investigate the perpetuation mechanisms, distribution, host specificity and transmission routes of pathogens in nature, as well as performing an exhaustive search for novel microorganisms that may potentially cause zoonoses in the future. In addition, strategies for the prediction and prevention of endemic infectious diseases will also be developed using a bioinformatic approach.

"Research into the prevention and control of zoonotic viral diseases"

- •Understanding the ecology of hemorrhagic fever viruses: identification of natural reservoirs
- ·Global surveillance of influenza
- •The molecular basis of filovirus pathogenesis: the role played by the function of viral glycoproteins
- •Experimental studies on novel immunization strategies against viral infection
- ·Understanding the host and viral factors involved in virus infection

TSUBOTA, Toshio

Professor, Lab. of Wildlife Biology and Medicine, Dept. of Environmental Veterinary Sciences, Graduate School of Veterinary Medicine



"Research in wildlife ecology and zoonosis control"

Wildlife often plays a key role in emerging and re-emerging zoonosis. Some creatures act as natural hosts of zoonoses in nature by maintaining pathogens, and new routes of infection are often established as a result of ecosystem imbalance and exploitation. The goal of the present study is therefore to clarify the relationships between wildlife biology (ecology) and infection by diseases in nature. The study will be conducted by 1) establishing methods for capture and immobilization, extracting samples and marking wild mammals and birds, and 2) telemetric tracking of wildlife for epidemiological surveying in zoonosis models.

ARIKAWA, Jiro

Professor, Dept. of Microbiology, Graduate School of Medicine



"Research in epidemiology of viral infectious diseases"

We studied serologic and genetic diagnostic methods of hantavirus infection (a typical rodent-borne viral zoonosis), hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), and applied the methods used in the epidemiological study of human and rodent reservoirs in several Asian countries. Through collaborative studies with researchers in countries where these endemics are found, we plan to clarify the epidemiologic status of hantavirus infection and establish such studies on a continued basis.

OHASHI, Kazuhiko

Professor, Lab. of Infectious Diseases, Dept. of Disease Control, Graduate School of Veterinary Medicine



"Research in epidemiology of avian infectious diseases"

Molecular epidemiological surveys of pathogenic viruses will be conducted on both domestic and wild birds including geese and ducks. For this purpose, molecular diagnostic methods will be developed to detect the genes of several kinds of virus from samples such as feathers and feces. Viruses thus detected will be characterized in detail and compared with those previously reported in order to determine their biological properties, including their pathogenicity to avian species.

ITO, Kimihito

Associate Professor, Dept. of Bioinformatics, Research Center for Zoonosis Control (from Jan.1,2011)



"Bioinformatics for zoonosis control"

The rapid development of molecular biology over the last two decades has accelerated the accumulation of results from genetic and experimental studies on zoonotic pathogens. The massive biological data sets now available enhance the chances of finding important factors that are essential for zoonosis control and have not been addressed so far. Through a fusion of bioscience and informatics, we will conduct comprehensive studies based on large-scale data sets detailing zoonotic pathogens to identify causative factors in infection, and intend to establish strategies to predict and prevent the occurrence and epidemic spread of zoonoses.

Immunological and Pathological Research Group

HORIUCHI, Motohiro

Professor, Lab. of Veterinary Hygiene, Dept. of Applied Veterinary Sciences, Graduate School of Veterinary Medicine



"Pathobiological research for zoonosis control"

We will concentrate on clarifying the molecular mechanisms that determine host-specificity, and on the tissue tropisms of pathogens such as viruses, bacteria, protozoa, parasites and prions. We will also focus on elucidating the molecular basis of zoonotic infection pathogenesis. Furthermore, we will make efforts to clarify the mechanisms of innate and acquired immunity against zoonotic pathogens. The outcomes of the research are expected to provide useful information on the development of diagnosis, preventive measures and therapeutics for zoonosis.

"Studies on the mechanism of prion propagation and pathogenesis of prion diseases"

Propagation and transmission of prion, the infections agent of prion diseases, thought to be associated with membrane trafficking, although the precise mechanism involved is unclear. Our focus lies in clarifying the molecular mechanisms of prion propagation within cells and prion transmission between cells. Microglial activation and astrocytosis, as well as the up-regulation of chemokines and cytokines, are common features of the neuropathological lesions associated with prion diseases. We also focus on understanding the mechanisms of such host responses in the pathogenesis of the diseases. In addition, we aim to establish the therapeutics for prion diseases based on the molecular mechanisms of prion propagation and pathogenesis.

SAWA, Hirofumi

Professor, Dept. of Molecular Pathobiology, Research Center for Zoonosis Control



"Investigation of molecular pathogenesis of viral diseases"

We have investigated the relationship between hosts and infectious pathogens using newly established molecular biological and cell biological approaches, and have examined the intracellular movement of virions using spatiotemporal imaging techniques. We have also found a therapeutic strategy involving siRNA and pharmaceutical reagents for the treatment of viral infectious diseases based on the results obtained from basic research. Recently, We have worked to identify natural reservoirs of hemorrhagic viruses mainly in the Republic of Zambia, Africa.

UMEMURA, Takashi

Professor, Lab. of Comparative Pathology, Dept. of Veterinary Clinical Sciences



"Investigation of neurotropic mechanisms of microorganisms and defense mechanisms of host immunity to the neurotropic pathogens"

The mechanisms behind the transneural spread of the rabies virus, the highly pathogenic avian influenza virus, the pseudorabies virus and the hemagglutinating encephalomyelitis virus will be compared and clarified to establish novel preventive and therapeutic measures for these diseases. In particular, priority will be given to the development and establishment of (1) therapy for rabid animals and humans, (2) an animal model of influenzal encephalopathy in childhood, and (3) demonstration of defense mechanisms of intrathecal immunization to neurotropic pathogens.

INABA, Mutsumi

Professor, Lab. of Molecular Medicine, Dept. of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine



"Development of molecular-based diagnostic tools for Prion diseases"

We have investigated physiological and pathobiological mechanisms for quality control and proteasomal degradation in the ER, membrane trafficking, association with partner proteins, and functional assembly into the plasma membrane of transmembrane proteins. We are also working on the mechanism behind the inherited structural diversity of the major transmembrane sialoglycoprotein found on the surface of erythroid cells. Based on the findings of these studies, we will analyze the cellular molecules that regulate or affect the intracellular turnover and trafficking of virus membrane proteins and/or the invasion of viruses and protozoan parasites.

Diagnostic and Therapeutic Research Group

SUZUKI, Yasuhiko

Professor, Dept. of Global Epidemiology, Research Center for Zoonosis Control



"Research in diagnosis and therapy of zoonosis"

Diagnostic and Therapeutic Research Group will develop novel strategies for diagnostic, therapeutic, and prophylactic methods, animal models for zoonosis research and technologies for the isolation and identification of pathogens.

"Study on the development of rapid diagnostic system of zoonoses"

- Establishment of sensitive detection methods for mycobacteria and their application to the detection of mycobacteria from animal and human specimens
- Development of rapid drug susceptibility testing for mycobacteria and its application to clinical isolates and clinical specimens
- Development of novel genotyping methods for mycobacteria and the molecular epidemiological study of mycobacteria transmission between human and animals
- Establishment of sensitive detection methods for leptospiras and their application to the detection of mycobacteria of animal, human and environmental origin

NOGUCHI, Masayuki

Professor, Division of Cancer Biology, Institute for Genetic Medicine



"Investigation of signal transduction and its application for therapy"

The PI3K-Akt network is activated by various cytokines or growth factors, and mediates intracellular signals to regulate a wide variety of cellular responses including anti-apoptosis, proliferation, cell cycling, protein synthesis, glucose metabolism and telomere activity. Genomic mutations (alterations of the PI3K-Akt regulatory network) underlie various human diseases including cancer, glucose intolerance (or diabetes mellitus), schizophrenia and/or autoimmune diseases. Recently, in addition to direct involvement in tumorigenesis through genetic alteration of human cancers, the PI3K-Akt network has also been found to underlie the clinical manifestation of various stages of viral infection. These include acute, latent or chronic infection from various sources such as the H5N1 virus, the Epstein-Barr virus, the Hepatitis C virus, the Hepatitis B virus and the Human Immunodeficiency Virus (HIV). We will investigate the PI3K-AKT network, which could underlie various phathological conditions of viral and/or bacterial infection. Directing anti-viral activity through the suppression of PI3K-Akt activity may provide opportunities to prevent viral infection, offering therapeutic potential in clinical usage.

MIYAZAKI, Tadaaki

Professor, Dept. of Bioresources, Research Center for Zoonosis Control



"Development of diagnostic methods and drugs for prevention and treatment of zoonoses"

Our work includes clarification of the mechanism behind infection and the proliferation of pathogens (or pathogenesis) in zoonoses. In particular, we aim to identify the host factors involved in the infection and proliferation of the influenza virus. In addition, we analyze the mechanisms and importance of apoptosis induction and cytokine production after viral infection, as well as host defense systems against pathogens. Finally, we aim to develop diagnostic methods and effective drugs for the prevention and treatment of zoonoses.

HIGASHI, Hideaki

Professor, Dept. of Immunology, Research Center for Zoonosis Control (from Jan.1,2011)



"Investigation of structure-activity relationship of molecules and their application for therapy"

Various mammalian animals are infected with bacteria of the Helicobacter genus, and such infection is thought to be associated with the development of intestinal diseases. H. pylori cagA-positive strains (which produce CagA proteins) are more virulent than cagA-negative strains, and infection with the cagA-positive strain greatly increases the risk of developing gastric carcinoma. We focus on the oncogenic mechanism of CagA proteins in terms of the mechanism of carcinogenesis initiated by H. pylori infection, and seek approaches for the prevention and treatment of cagA-positive H. pylori infection.

Location





Graduate School of Medicine

Global COE Office





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