Research Center for Asian Infectious Diseases
アジア感染症研究拠点

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Research Center for Asian Infectious Diseases has established three project joint laboratories (one in Tokyo; two joint labs in Beijing) and a collaborative program (Harbin), supported by AMED, CAS, and CAAS. The center is conducting research on emerging and reemerging infections, aiming to translate its basic studies into practical use. And the project intends to train and educate young Japanese and Chinese scientists for the future generation.

BACKGROUND

China is an important neighbor of Japan, with geopolitical and economic interdependence. And it contains hot spots for emerging and reemerging infections, as exemplified by the occurrence of SARS coronavirus that shocked the world in 2003 and endemic avian influenza virus occasionally jumping from bird to human. The carrier rate of hepatitis viruses is very high and HIV infection is rapidly increasing. In the early 2000's the Institute of Medical Science, the University of Tokyo, (IMSUT) was looking for appropriate counterparts in China to strengthen the studies of emerging and reemerging infections.

IMSUT established three collaboration sites in fiscal 2005 in China, two in Beijing and one in Harbin, and had been conducting China-Japan research collaboration, for two 5-year terms (fiscal 2005-2010; 2010-2015), supported by the Ministry of Education, Culture, Sports, Science and Technology under the directorship of Aikichi Iwamoto, former project director. IMSUT thus set up a new sustainable system that allowed IMSUT scientists to work in China, along with Chinese scientists, focusing on the studies of emerging and reemerging infections. In 2015 Yasushi Kawaguchi succeeded A. Iwamoto as project director and launched the project *China-Japan Research Collaboration on Defense against Emerging and Reemerging Infections,* a new 5-year J-GRID program of Japan Agency for Medical Research and Development (AMED).

In 2005 IMSUT had founded two joint laboratories in collaboration with the Institute of Biophysics (IBP) and Institute of Microbiology (IM), which belong to the Chinese Academy of Sciences (CAS), a large national institution consisting of more than 100 research institutes all over China. IMSUT has dispatched Zene Matsuda and Takaomi Ishida to IBP and IM, respectively, as principal investigators (PIs). Along with their Japanese and Chinese staffs, these PIs are conducting basic and translational studies of HIV, MERS coronavirus, dengue virus and norovirus. In 2015 IMSUT has set up another

project laboratory in Tokyo, whose studies complement those in Beijing. The activities of the three laboratories are under Jun-ichiro Inoue's direction. IMSUT is also conducting a joint research program on avian influenza virus between Yoshihiro Kawaoka at IMSUT and Hualan Chen at the Harbin Veterinary Research Institute (HVRI) of Chinese Academy of Agricultural Sciences. The activities in Beijing and Harbin are supported by Mitsue Hayashi of the Beijing Project Office.

This project, making the most of the opportunity of collaboration with the highly advanced Chinese institution, aims to translate our basic studies into practical use in future. During the course of the collaboration the project intends to train and educate young Chinese and Japanese scientists for the future generation and hopes to contribute to the friendship between the two peoples.

PROJECT LABORATORIES AND PROGRAM

Y. Kawaguchi (Director of Research Center for Asian Infectious Diseases; Project Director) manages the Center and the AMED-supported Project, which includes the domestic and overseas laboratories and program. He coordinates their activities and decides the direction of research. He and his group conduct studies of molecular virology and immunology of herpes virus in the Research Center for Asian Infectious Diseases.

a. Project Laboratory at IMSUT

J. Inoue and his group at IMSUT are trying to find small molecular weight compounds that inhibit the membrane fusion caused by emerging viruses such as HIV-1, MERS coronavirus (MERS-CoV) and Dengue virus (DENV), in close collaboration with Z. Matsuda's group at IBPCAS (see below). For MERS-CoV, they developed a cell-based fusion assay for MERS S protein in a TMPRSS2-dependent manner, using cell lines expressing *Renilla* luciferase (RL)-based split reporter proteins, and optimized it for a 384-well format. For HIV, they also developed cell-based fusion assays for HXB2-env (CXCR4-tropic) and JRFL-env (CCR5-tropic). Using these assays, they screened last year 1,017 FDA-approved drugs (ref. Annual Report 2016). In addition they screened this year 9,600 compounds from *Drug Discovery Initiative, The University of Tokyo,* to find specific inhibitors of the fusion induced by MERS-CoV or HIV-1, obtaining several candidate compounds. For DENV, they are establishing the cell fusion assay for a 384-well format.

b. Joint Laboratory at IBPCAS

Z. Matsuda and his group at IBPCAS are conducting research on structure-function relationship of the viral envelope proteins derived from HIV-1 and DENV to develop peptide inhibitors of their membrane fusion. They are trying to develop a screening method to find the peptides that specifically bind to the viral envelope proteins. Candidate peptides will be evaluated by the cell-cell membrane fusion assay called DSP assay based on split *Renilla* luciferase (RL) reporter proteins. They are also collaborating with J. Inoue's group on improving the virus-cell infection assay of HIV-1.

c. Joint Laboratory at IMCAS

To achieve a sterilizing cure of HIV-1 infection, all the HIV-1 in the body needs to be eradicated. However, the current combination anti-retroviral therapy (cART) alone cannot eradicate the latent HIV-1 in reservoirs. To overcome this problem, the "Shock and Kill" strategy that involves the purge of HIV-1 from reservoir cells by re-activation followed by the cART has been proposed. T. Ishida and his group are studying the mechanism of latent HIV-1 infection and established model cell lines harboring latent HIV-1 provirus. Using these cell lines, they identified several potential activators of the latent HIV-1. Such activators may be applied to the "Shock and Kill" strategy.

d. Collaborative research program with HVRI

Since 2013, avian influenza A viruses of the H7N9 subtype (A(H7N9)) have caused sporadic infections in humans in China. In 2009, the novel influenza "pandemic (H1N1) 2009" emerged and spread rapidly throughout the world. In addition, since 2003, highly pathogenic avian H5N1 influenza viruses have continued to cause unprecedented global outbreaks with high case fatality rates in humans. For these reasons, HVRI (Director, Zhigao Bu) has been conducting collaborative research on influenza virus isolates from all over Asia.

HVRI focuses on avian influenza viruses (AIVs) that are circulating in Chinese wild waterfowl, domestic poultry, and swine. Specifically, Y. Kawaoka and his group study type A influenza viruses from wild birds, waterfowl, poultry, and swine, with an emphasis on viral pathogenicity in various hosts, viral evolution, and viral prevalence.

Their major findings this year include: *(1) Characterization of a highly pathogenic avian H7N9 influenza virus isolated from a human in China.* Highly pathogenic avian influenza (HPAI) H7N9 viruses have emerged and raised concerns of a pandemic. Y. Kawaoka's group characterized an HPAI H7N9 virus isolated from a human in China. This virus transmitted among ferrets without prior adaptation and caused lethal infection in the animals, demonstrating its pandemic potential and the need for surveillance. *(2) Characterization of a feline influenza*

A(H7N2) virus. From December 2016 to February 2017, influenza A viruses of the H7N2 subtype infected over 500 cats in animal shelters in New York, demonstrating the virus transmission among cats. A veterinarian who treated the animals also became infected with feline influenza A(H7N2) virus and experienced respiratory symptoms. Y. Kawaoka's group demonstrated that feline H7N2 viruses could replicate in the respiratory organs of mice, ferrets, and cats without causing severe lesions. Direct contact transmission of feline H7N2 viruses was detected in ferrets and cats; in cats, exposed animals were also infected via respiratory droplet transmission. These results suggest that the feline H7N2 viruses could spread among cats and also infect humans. Outbreaks of the feline H7N2 viruses could, therefore, pose a risk to public health.

IMSUT PROJECT OFFICE

The office (M. Hayashi) supports the activities of the two joint laboratories in Beijing and one joint research program in Harbin. It serves as Secretariat for Steering Committee Meeting and files MOU and Minutes. It helps scientists visiting the joint laboratories and program for collaborative research. It has been gathering the information about emerging infections in China from the Chinese mass media and official announcements, and the gathered information (in Japanese) has been presented and updated on the website of the Project (http://www.rcaid.jp/).

Publications

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