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

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The Institute of Medical Science, The University of Tokyo (IMSUT) has established Japan-China joint laboratories for research on emerging and re-emerging infectious diseases in Asia, in collaboration with the Chinese Academy of Sciences and Chinese Academy of Agricultural Sciences. In the laboratories, Japanese and Chinese scientists conduct research on the viral pathogenicity, the genetic variation of viruses in the field, the structure-function relationship of viral proteins and so on.

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 joint laboratory in Tokyo, whose studies complement those at Beijing. The IMSUT joint laboratory coordinates the activities of the three laboratories, which 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.

JOINT LABORATORIES AND PROGRAM

a. Joint Laboratory at IMSUT

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 joint 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.

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 Matsuda's group at IBPCAS (see below). They are adapting the split protein-based cell-cell fusion assay, called the DSP (dual split protein) assay, to future high-throughput screening of candidate compounds. They have established several effector and target cell lines that express the respective viral envelope proteins and corresponding receptors for both HIV-1 and MERS-CoV. Using these cell lines, they have optimized the assay conditions for future screening. For DENV, they are conducting preliminary experiments for the cell fusion assay.

b. Joint Laboratory at IBPCAS

Z. Matsuda and his group at IBPCAS are trying to establish cell-cell fusion assay systems for HIV-1, MERS-CoV and DENV. In IBP, they are conducting research on structure-function relationship of the viral envelope proteins derived from these viruses to develop peptide inhibitors of membrane fusion. They are also exploring the possibility of developing a new set of split reporter proteins for monitoring membrane fusion.

c. Joint Laboratory at IMCAS

The framework of collaboration with IMCAS was re-organized, starting new programs. T. Ishida and his group focus on studying activation of dormant HIV-1 provirus, which may help drive the persisting virus out of the body and potentially useful in future treatment. A cell system harboring dormant provirus (replication incompetent) to monitor the activation of the LTR in vitro was established and will soon be ready to be used for screening of factors affecting HIV-1 provirus activation. Also, preparation for the molecular epidemiological study of norovirus in China is in progress.

d. Joint research program with HVRI

Since 2013, avian influenza A virus 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 has focused on avian influenza viruses (AIVs) circulating in Chinese wild waterfowl and domestic poultry. 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 in 2015 include: *(1) Characterization of Eurasian avian-like H1N1 swine influenza viruses*. They performed extensive influenza surveillance in pigs in China and isolated 228 influenza viruses from 36,417 pigs. They found that 139 of the 228 strains from pigs in 10 provinces in China belong to the Eurasian avian-like H1N1 (EAH1N1) lineage. These viruses formed five genotypes, with two distinct antigenic groups. Importantly, the EAH1N1 SIVs preferentially bound to human-type receptors, and 9 of the 10 tested viruses transmitted in ferrets by respiratory droplet. They found that some Chinese individuals had neutralizing antibodies against one of the EAH1N1 virus, but none of them had such antibodies against another virus that belongs to the other antigenic group. Their study shows the potential of EAH1N1 SIVs to transmit efficiently in humans and suggests that immediate action is needed to prevent the efficient transmission of EAH1N1 SIVs to humans. *(2) Identification of mammalian-adapting mutations in the polymerase complex of an avian H5N1 virus*. They used a high-throughput screening approach to identify novel mutations in the polymerase genes of an avian H5 N1 virus that confer efficient polymerase activity in mammalian cells. Several of the identified mutations increase viral replication in mammalian cells

and virulence in infected mice compared with the wild-type virus. The identification of amino acid mutations in avian H5N1 virus polymerase complexes that confer increased replication and virulence in mammals is important for the identification of circulating H5N1 viruses with an increased potential to infect humans.

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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