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 operates two project laboratories (one in Tokyo; one joint lab 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 initially 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 5-year J-GRID program of Japan Agency for Medical Research and Development (AMED). In 2020 based on the results of the previous five years, he launched another project *Studies to Control Emerging, Re-emerging and Imported Infectious Diseases to Be Conducted in International Collaboration Sites in China* under a 5-year AMED program *Japan Program for Infectious Diseases Research and Infrastructure*.

In 2005 IMSUT had founded two joint laboratories in collaboration with 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 Jin Gohda to IM as a principal investigator (PI). Along with his Chinese staffs, PI is conducting basic and translational studies of HIV, MERS coronavirus, dengue virus and SARS-CoV-2. In 2015 IMSUT has set up another project laboratory in Tokyo, whose studies complement those in Beijing. IMSUT is also conducting a

joint research program on avian influenza virus between Yoshihiro Kawaoka at IMSUT and Hualan Chen at 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 our 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 and Joint Laboratory at IMCAS

Many enveloped viruses, such as HIV-1, flavivirus, herpes simplex virus, and coronavirus, are pathogenic and of clinical importance. J. Gohda's and Y. Kawaguchi's groups are conducting a basic research on the development of antiviral therapy for infectious diseases caused by enveloped viruses.

Severe acute respiratory syndrome coronavirus 2 (SRAS-CoV-2) is the causative virus of Coronavirus disease 2019 (COVID-19), which has spread worldwide since the first case was reported in China in December 2019. The rapid development of antiviral drugs and vaccine against SARS-CoV-2 infection is needed for bringing an ongoing pandemic of COVID-19 to an end. J. Gohda and his group established a dual split protein-based cell fusion assay for SARS-CoV-2 spike protein to evaluate the antiviral activities of compounds and antibodies against SARS-CoV-2. We found by using the fusion assay that an existing Japanese pancreatitis drug, nafamostat strongly prevents viral entry of SARS-CoV-2 by inhibiting a serine protease, TMPRSS2, which is crucial for membrane fusion between SARS-CoV-2 and its target cells. Furthermore, we found that several compounds inhibit viral entry of SARS-CoV-2. This year, we demonstrated that two existing drugs significantly prevent infection with SARS-CoV-2 mutants, including Omicron, by inhibiting TMPRSS2-dependent cell surface entry and TMPRSS2-independent endosomal entry. These compounds might lead to the development of an antiviral drug against SARS-CoV-2 entry both through the cell surface pathway and the endosomal pathway. On the other hand, SARS-CoV-2 Omicron variant has been recently reported to exhibit decreased usage of the TMPRSS2-mediated cell surface entry pathway and increased usage of the endosomal entry pathway, which might cause altered cell tropism and less tissue damage. In addition, J. Gohda's group previously found that metalloproteinases are specifically involved in SARS-CoV-2 viral cell surface entry in some cell-types. This year, we performed comprehensive analyses of the usage of viral entry pathways, including the third entry pathway mediated by the host metalloproteinases, in Omicron infection. The study using various cell types showed that Omicron displayed the enhanced endosome entry and the reduced metalloproteinase-dependent as well as TMPRSS2-dependent cell surface entry. Furthermore, we showed that Omicron's fusogenic activity mediated by metalloproteinases was markedly reduced. We also demonstrated that the H655Y mutation in the Omicron spike determined its relative usage of the three entry pathways. These finding may not only clarify the biological and pathological phenotypes of Omicron, but increase the understanding of disease progression in infections with other SARS-CoV-2 variants.

The use of combination anti-retroviral therapy (cART) has considerably contributed to preventing the development of AIDS in patients infected with human immunodeficiency virus type 1 (HIV-1). However, HIV-1 latent reservoirs harboring silenced but replication-competent provirus are a major obstacle against viral eradication in the infected patients. The "shock and kill" strategy, which is one of promising approaches to a cure of HIV-1 infection, is aimed to reactivate the latent provirus by treatment with latency reversing agents (LRAs), which is called "shock", in the presence of antiretroviral drugs. Some drugs have been so far identified as an LRA. However, no drugs that cause cell death of HIV-1 latent reservoirs, which is called "kill", has not been identified yet. J. Gohda and his group has identified several existing drugs as a new LRA candidate. This year, we tried to clarify the molecular mechanism of re-activation of latent HIV-1 provirus by these drugs. As a result, one of the candidate drugs may re-activate HIV-1 proviral transcription through the different mechanism by which the existing LRAs induce the proviral re-activation. Furthermore, we are currently trying to identify compounds that block the release of HIV-1 viral particles from infected cells to "kill" the reactivated reservoirs by a cytopathic effect through accumulation of cytotoxic viral proteins in the cells without releasing infectious viral particles.

b. Joint Laboratory at IBPCAS

The Joint Laboratory at IBPCAS was closed in

March 2020. However, the research collaboration and academic exchange between IMSUT and IBPCAS is still ongoing.

c. Collaborative research program with HVRI

At the end of 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) was detected in Wuhan, China, that spread rapidly around the world, with severe consequences for human health and the global economy. In China, highly pathogenic avian influenza (HPAI) H5N1 virus transmitted to humans in 1997; since 2013, low pathogenic avian influenza A H7N9 viruses have caused sporadic infections in humans; and in 2016, HPAI H7N9 viruses emerged raising concerns of a pandemic. For these reasons, HVRI (Director, Zhigao Bu) has been conducting collaborative research on influenza virus, SARS-CoV-2, and other emerging viruses from all over Asia.

HVRI focuses on avian influenza viruses that are circulating in Chinese wild waterfowl, domestic poultry, and swine. Specifically, Y. Kawaoka and his group study type A influenza viruses and SARS-CoV-2 viruses, with an emphasis on viral pathogenicity in various hosts, viral evolution, and viral surveillance.

The major findings this year are: (1) Our routine surveillance in China indicated that the Eurasian avian-like H1N1 (EA H1N1) swine influenza viruses circulated widely in pigs, and obtained different internal genes from different swine influenza viruses, forming various new genotypes. We found that a naturally isolated swine influenza reassortant, A/swine/Liaoning/265/2017, a representative strain of one of the predominant genotypes in recent years, is lethal in mice and transmissible in ferrets due to the acquisition of key mutations in PA. Our study provides important insights for monitoring field strains with pandemic potential. (2) We evaluated the replicative ability and pathogenicity of sublineages BA.1, BA.2, BA.4, and BA.5 of SARS-CoV-2 Omicron variants in wild-type Syrian hamsters, human ACE2 (hACE2) transgenic hamsters, and hACE2 transgenic mice. We observed no obvious differences among BA.1, BA.2, BA.4, and BA.5 isolates in terms of growth ability or pathogenicity in rodent models, but these isolates were less pathogenic than a previously circulating Delta (B.1.617.2 lineage) isolate. In addition, we analyzed the efficacy of antiviral drugs and antibodies against Omicron variants. The susceptibilities of BA.1, BA.2, BA.2.75, BA.4.6, BA.5, BQ.1.1, and XBB to remdesivir, molnupiravir, and nirmatrelvir were similar to those of the ancestral strain and other variants of concern. The effectiveness of monoclonal antibodies (REGN10987–REGN10933, COV2-2196–COV2-2130, and S309) varied with the type of omicron strain. None of the monoclonal antibodies tested was effective against all omicron strains.

IMSUT PROJECT OFFICE

The office (M. Hayashi) supports the activities of the joint laboratory in Beijing and the joint research program in Harbin. It serves as Secretariat for Steering Committee Meeting and files MOU and Minutes. It helps scientists visiting the joint laboratory/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/).

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