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

Enveloped viruses, including HIV-1, Flaviviruses, Herpes Simplex Viruses, and Coronaviruses, exhibit pathogenicity and are clinically significant. The J. Gohda and Y. Kawaguchi research groups are conducting studies aimed at the development of antiviral molecules targeting enveloped viruses, including SARS-CoV-2, as well as the exploration of molecules for the reactivation of HIV-1 reservoirs.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative virus for Coronavirus Disease 2019 (COVID-19) and has globally expanded since the first reported patient in December 2019 in China. To bring an end to the ongoing COVID-19 pandemic, development of antiviral drugs and vaccines targeting SARS-CoV-2 infection is imperative. We have established a dual split protein-based cell fusion assay utilizing the SARS-CoV-2 spike protein to evaluate the antiviral activity of several molecules, advancing the screening of antibodies and small molecular compounds. This year, we have established novel neutralizing antibodies that exhibit neutralizing activity without binding to the conventional antibody pharmaceutical target, the Receptor Binding Domain (RBD). These antibodies target conserved regions, even in related coronaviruses and SARS-CoV-2 variants, suggesting potential long-term utility. Moreover, these conserved regions may serve as candidates for inducing effective neutralizing antibodies through vaccination. From the analysis of small molecular compounds, multiple inhibitors against TMPRSS2, a crucial host protease for virus infection, were identified from synthetic compounds. Additionally, two compounds inhibiting virus entry and proliferation within cells were identified from subtropical plant extracts. These inhibitory molecules not only hold promise for future therapeutic development but also play a crucial role in elucidating the infection mechanisms of SARS-CoV-2. The elucidation of the target molecules of these agents is expected to contribute to the discovery of new infection mechanisms and therapeutic targets.

The utilization of combination antiretroviral therapy (cART) has significantly contributed to impeding the progression to acquired immunodeficiency syndrome (AIDS) in individuals infected with human immunodeficiency virus type 1 (HIV-1). Nevertheless, the presence of latent reservoirs of HIV-1, housing silenced yet replication-competent provirus, constitutes a formidable barrier to viral eradication in affected individuals. The "shock and kill" strategy, a promising approach toward curing HIV-1 infection, seeks to reactivate latent provirus through treatment with latency reversing agents (LRAs), denoted as "shock," in conjunction with antiretroviral drugs. While several drugs have been identified as LRAs, no drug has been clinically applied to date. We have identified multiple existing drugs as novel LRA candidates. In this year, our efforts have focused on elucidating the molecular mechanism of reactivation of latent HIV-1 provirus by these drugs. Our findings suggest that one of the candidate drugs may reactivate HIV-1 proviral transcription through a distinct mechanism from the established LRAs that induce proviral reactivation. We are currently engaged in identifying target proteins and advancing their functional analysis. Furthermore, we are analyzing the synergistic interactions between novel drugs and existing LRAs, aiming to establish methods that induce more effective "shock". Through these analyses, there is a prospect for the future depletion of HIV reservoirs in patients, thereby offering the potential for a complete treatment of AIDS.

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 vi-

rus 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) We isolated 77 HPAI viruses during routine surveillance in live poultry markets in northern provinces of Vietnam from 2018–2021. These viruses were genetically different from those in other parts of the world. These viruses do not encode major determinants of mammalian adaptation but possess amino acid substitutions that may affect viral receptor-binding, replication, or responses to human antiviral factors. Our ongoing surveillance of HPAI viruses in several parts of the world is important to monitor the evolution of these viruses. (2) We analyzed the efficacy of antiviral drugs and antibodies against Omicron variants. The susceptibilities of CH.1.1 and XBB.1.5 to remdesivir, molnupiravir, nirmatrelvir, and ensitrelvir were similar to those of the ancestral strain and other variants of concern. The effectiveness of monoclonal antibodies (i.e., sotrovimab, bebtelovimab, casirivimab/imdevimab, and tixagevimab/cilgavimab) varied with the omicron strain tested. None of these monoclonal antibodies was effective against CH.1.1 or XBB.1.5. In addition, we found that a bivalent vaccine (ancestral and BA.4/5) can improve humoral responses to both viruses.

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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