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*, which was further extended in 2025 until the end of fiscal year 2026.

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. In 2015, IMSUT established another project laboratory in Tokyo, whose studies complement those in Beijing. IMSUT has dispatched

Xuenan Xuan to IMCAS as a principal investigator in 2025. Together with Chinese staff, he conducts epidemiological investigations of tick-borne viral infections and basic studies on enveloped viruses, focusing on infection mechanisms and therapeutic development. 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 institutions, 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

Ticks transmit pathogens such as viruses and protozoa between wildlife/livestock and humans, and the resulting zoonotic diseases represent a major social concern. To respond effectively to the introduction of these pathogens into Japan from continental regions such as China and Russia, epidemiological surveillance of these pathogens in affected local areas, together with analyses of their infection mechanisms and the development of effective therapeutics, is essential. Our laboratory conducts epidemiological investigations of these zoonotic infections in China and, in parallel, advances research toward the development of antiviral molecules targeting enveloped viruses—shared challenges for Japan and China—including flaviviruses, herpes simplex viruses, and coronaviruses.

This year, we advanced epidemiological investigations of tick-borne zoonotic infections in China's Xinjiang Uygur Autonomous Region. The region borders eight countries, making it an important area for understanding outbreaks and transmission patterns across northwestern China and Central Asia. Using ticks collected locally and blood samples from livestock, we assessed viral gene detection, aiming to generate foundational data to characterize circulating pathogens and strengthen preparedness for cross-border pathogen introduction. We also identified 11 subtropical plant-derived samples from Okinawa with anti–SARS-CoV-2 membrane-fusion inhibitory activity. Compounds isolated from these samples were found to target host factors essential for infection and to be effective against multiple SARS-CoV-2 variants. In addition, we advanced mechanistic studies of neutralizing antibodies that recognize regions outside the RBD and demonstrated a unique inhibitory mechanism in which antibody binding induces large-scale conformational changes across the spike protein, thereby blocking key steps in infection. Collectively, our field-based surveillance in Xinjiang provides epidemiological evidence that supports risk assessment and public health preparedness for tick-borne zoonoses; by addressing a shared challenge for Japan and China in close collaboration with local researchers, it also helps build a sustainable, long-term Japan–China research partnership. In parallel, our identification and mechanistic characterization of SARS-CoV-2 entry inhibitors—including membrane-fusion inhibitory compounds and non-RBD neutralizing antibodies—provide a foundation for future antiviral development and deepen our understanding of viral entry mechanisms.

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.

We made two major findings this year. First, to ad-

dress the need for broadly protective COVID-19 vaccines, we developed an attenuated SARS-CoV-2 vaccine virus lacking the open reading frames of the envelope (E) and membrane (M) proteins. This vaccine virus (ΔEM) replicates only in a cell line stably expressing E and M (i.e., not in wild-type cells). Vaccination with ΔEM elicits a CD8 T-cell response against the viral spike and nucleocapsid proteins. Two vaccinations with ΔEM provide better protection of the lower respiratory tissues than a single dose against the Delta and Omicron XBB variants in hamsters. Moreover, ΔEM is effective as a booster in hamsters previously vaccinated with an mRNA-based vaccine, providing higher levels of protection in respiratory tissues compared to the mRNA vaccine booster. Collectively, our data demonstrate the feasibility of a SARS-CoV-2 ΔEM vaccine candidate virus as a vaccine platform. Second, in response to recent outbreaks of highly pathogenic avian influenza A(H5N1) virus in dairy cattle, we examined the replication of bovine H5N1 viruses in ex vivo explant cultures of mammary gland and teat tissues from lactating cows. A bovine H5N1 isolate replicated more efficiently than avian H5N1 or human H1N1 pandemic viruses, particularly in the gland and teat cistern epithelium. Both avian- and human-type influenza virus receptors were broadly expressed in these tissues, indicating susceptibility to infection. These findings suggest that bovine-adapted H5N1 viruses can efficiently replicate in mammary tissues and that the teat canal may serve as an important route of viral entry, providing insight into viral tropism and transmission in dairy cattle.

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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