No.	K25-3118	
Project Title	Development of a Universal Influenza Vaccine	
Principal Investigator	Miyu Moriyama (Yale University・Associate Research Scientist)	
Project Member(s)	**IMSUT Host Researcher**	Takeshi Ichinohe (The Institute of Medical Science, The University of Tokyo・Associate professor)
	Project Member (s)	Manabu Igarashi (Division of Global Epidemiology, International Institute for Zoonosis Control, Hokkaido University・Associate Professor)
	Project Member (s)	Toshiro Hirai (Laboratory of Nano-Design for Innovative Drug Development, Graduate School of Pharmaceutical Sciences, Osaka University・Lecturer)
	Project Member (s)	Shuzo Urata (National Research Center for the Control and Prevention of Infectious Diseases (CCPID), Nagasaki University・Associate Professor)

(Form 2)

Principal Investigator
Takeshi Ichinohe

IMSUT International Joint Usage/Research Center Project <Domestic>

Joint Research Report (Annual/Project Completion)

Annual Report

Report

The continuing pandemic potential of respiratory viruses remains a serious threat to public health, as evidenced by the global impact of the ongoing SARS-CoV-2 pandemic. As of December 8, 2024, over 777 million people have been infected with SARS-CoV-2, and more than 7 million people have died from COVID-19 worldwide. Respiratory viruses spread by direct contact, fomite transmission, or airborne transmission and are transferred to mucosal surfaces of exposed individuals. Thus, mucosal antiviral IgA play an important role in protecting against respiratory virus infection by blocking virus attachment to and release from host cells and by activating antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and the complement pathway.

Mounting evidence indicates that antiviral respiratory IgA is more effective and cross-protective against homologous and heterologous influenza virus infections than circulating IgG antibodies induced by parenteral vaccines, probably due to the increased avidity resulting from its multimeric nature. Similarly, respiratory antiviral IgA induced by intranasal vaccination plays an important role in protection against SARS-CoV-2 infection by reducing the viral load, disease severity, and airborne transmission. Gut microbiota and MyD88 signaling are essential for the induction of the virus-specific nasal and salivary IgA antibodies after respiratory influenza virus infection. In contrast, the role of innate immune signals required for the induction of the virus-specific mucosal antibodies to SARS-CoV-2 infection remains unknown.

Mouse-adapted SARS-CoV-2 variants are useful for studying vaccine development and the viral pathogenesis. Here we establish mouse-adapted SARS-CoV-2 alpha, gamma, and omicron BA.1 variants. By using the mouse-adapted SARS-CoV-2 variant, we show that the levels of antiviral IgA in the respiratory tract correlate with cross-protection against heterologous SARS-CoV-2 infection. In addition, we demonstrate that MyD88 and MAVS signaling play a role in the induction of the memory IgA response following intranasal booster with unadjuvanted Spike protein in mice recovered from the SARS-CoV-2 infection. These findings provide a useful basis for the development of effective mucosal vaccines against heterologous SARS-CoV-2 infection.