学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Exploring the usage of inactivated whole virus particle vaccines for influenza and COVID-19

（インフルエンザおよびCOVID-19不活化ウイルス全粒子ワクチンにより誘導される免疫効果の検討）

Influenza and coronavirus disease 2019 (COVID-19) are important since these diseases provoked severe pandemics that have caused enormous damages globally. Worldwide, approximately, 3–5 million people are infected each year with seasonal influenza viruses while as of June 2023, severe acute respiratory syndrome virus 2 (SARS-CoV-2) has claimed over 6.9 million lives and infected over 767 million people since its emergence in 2019. The co-circulation of seasonal influenza viruses with SARS-CoV-2 is particularly dreadful due to the unpredictability of the emergence of immune-escaping variants/subtypes. Accordingly, the World Health Organization (WHO) recommends vaccination to control the prevalence of both diseases.

Although seasonal influenza and COVID-19 vaccines are available, they have several issues that need to be addressed. The SV, for example, is broadly used to prevent seasonal influenza but induces a poor cross-reactive immune response and its immunogenicity can be modest in vulnerable groups such as children and the elderly. Messenger mRNA (mRNA) vaccines on the hand played a crucial role in impeding the spread of SARS-CoV-2. While they are quick and easy to manufacture once the sequence of the epitope is determined, they have a challenge of maintaining the cold chain for storage and transportation and they cause marked adverse effects such as high fever and muscle aches. In this study, the usage of the inactivated whole virus particle vaccine (WPV) to solve issues of current seasonal influenza and mRNA vaccines was explored.

In Chapter 1, the cross-immunogenicity and protectivity of WPV and SV of A/California/7/2009 (X-179A) (H1N1) pdm09 against heterologous influenza viruses; A/Singapore/GP1908/2015 (IVR-180) (H1N1) pdm09 [A/Singapore (H1N1)], A/Brisbane/02/2018 (IVR-190E) (H1N1) pdm09 [A/Brisbane (H1N1)], and A/duck/Hokkaido/Vac-3/2007 (H5N1) [A/Hokkaido (H5N1)] were investigated *in vivo.* After challenge with A/Singapore (H1N1), WPV conferred better protection than SV in mice. WPV also induced anti-HA antibodies against A/Singapore (H1N1) and anti-NA antibodies against A/Singapore (H1N1), A/Brisbane (H1N1),

and A/Hokkaido (H5N1), while SV induced only anti-HA antibodies against A/Singapore (H1N1). The use of WPV could potentially reduce the impact of immune evasion not only by antigenically drifted seasonal influenza strains but also by pandemic viruses of related subtypes to contemporary influenza strains.

In Chapter II, influenza WPV (Flu WPV) and COVID-19 WPV (Co WPV) were prepared and co-formulated to produce a two-in-one influenza/COVID-19 WPV (Flu/Co WPV). Serum analysis from the vaccinated mice revealed that a single dose of Flu/Co WPV induced high levels of neutralizing antibodies against both viruses, similar to those induced by either type of WPV alone. Moreover, upon infection with either virus, mice vaccinated with Flu/Co WPV showed no weight loss, significantly reduced lung tissue damage and virus titers, and lower proinflammatory cytokine expression as observed in those with individual WPVs infected with homologous virus. These results suggest that a single dose of two-in-one WPV provided efficient protection against both SARS-CoV-2 and influenza virus infections without apparent interference from each other in mice.

Therefore, due to the advantages of WPV including potent immunogenicity, safety and ease of handling, WPV could potentially resolve issues of current seasonal influenza and COVID-19 vaccines.