Development of Low-Inflammatory mRNA Vaccines Based on Lipid Materials with Intracellular Environmental Responsiveness and Destabilization.

Takayuki Yoshioka／Osaka University

Vaccines composed of mRNA encapsulated in lipid nanoparticles (mRNA-LNP) are expected to be a highly effective modality that can contribute to the 100 Days Mission. However, they induce frequently side effects such as fever, swelling at the vaccination site, and fatigue caused by the production of inflammatory cytokines. As this could trigger vaccine hesitancy, it is essential to reduce the side effects while maintaining the efficacy

It was observed that $LNP_{ssPalmO}$, prepared using the unique lipid material can exhibit high mRNA-transfection efficiency. This study will attempt to develop a vaccine for the highly pathogenic avian influenza virus (H5N1 virus) and demonstrate that mRNA-$LNP_{ssPalmO}$ can induce antibody production and T-cell response in mice that are in intensity equal to or greater than those induced by LNPs with the same composition (LNP_{SM-102}) as that of the COVID-19 mRNA vaccine developed by Moderna, while strongly inhibiting infection.

Furthermore, $LNP_{ssPalmO}$ induced a significantly lesser production of inflammatory cytokines and chemokines compared to LNP_{SM-102}, which are the main causes of adverse reactions. This study aims to develop a novel mRNA-LNP with reduced side effects with an equivalent vaccine efficacy compared to existing products, by utilizing our unique $LNP_{ssPalmO}$. Initially, establishment of mRNA and formulation production methods, non-clinical trials using animals, and manufacture of investigational drugs for mRNA-$LNP_{ssPalmO}$ are planned. Then, the phase I investigator-initiated, randomized, observer-blind, and placebo-controlled trial will be conducted at the Osaka University Hospital to evaluate its safety, tolerability, and immunogenicity. The proprietary patents for the manufacturing of ssPalmO and LNP are held by us, enabling the building of a new LNP modality based on technology developed by academia.

The study is being carried out mainly by the Research Center for Advanced Modalities and Drug Delivery System at Osaka University, which has established a strong industry-academia collaboration. It is expected to significantly contribute to improving the research standards and technological advancement of vaccine development in Japan, and lead to the development Japanese-made vaccines using domestic technology, without relying on foreign-made vaccines in the future. Additionally, mRNA-$LNP_{ssPalmO}$ has fewer side effects than other types of mRNA-LNP, so it can be used not only in emergencies but also in normal situations. It is expected to contribute to the international competitiveness of mRNA-LNP-based vaccine development in Japan.