Research and development of RNA vaccine modality for rapid induction of neutralizing antibody responses

Takayuki Matsumura／National Institute of Infectious Diseases

In the COVID-19 pandemic, the mRNA-LNP vaccine, which significantly shortened the time required to develop vaccines against novel pathogens, was the first to demonstrate its efficacy. However, more than two doses were required to increase neutralizing antibody titers, with relatively high incidences of adverse events. There is also no guarantee that current vaccine platforms will be effective in the future, with some cases, such as the H7N9 influenza virus split vaccine, demonstrating insufficient antigenicity (Mulligan MJ, et al. JAMA. 2014). Because vaccines that rapidly induce neutralizing antibodies in a single dose while minimizing the risk of adverse events are desirable for future novel pandemic responses, this study aims to develop a fast-acting, low-reactogenicity vaccine designed to rapidly and maximally elicit immunity in the population. Specifically, (1) appropriate T cell epitopes added to the antigen can activate existing memory helper T cells to rapidly and efficiently induce the desired neutralizing antibodies, and (2) an mRNA-LNP vaccine that can be rapidly developed during pandemics is selected as the modality, however, we aim to develop a vaccine with reduced reactogenicity to reduce the frequency of adverse events compared to current vaccines. Two types of SARS-CoV-2 spike T-cell epitopes, which are more active than pan-HLA-DR epitope peptides (PADRE) (Alexander J. et al. Immunity. 1994) in an experimental system using PBMC from COVID-19 vaccinees, are being identified. Since both of these two epitopes were suggested to be highly directed to HLA-DP, we are now considering designing epitope pan-HLA-DP epitope peptides (PADPE) that can target wider ranges of memory T cells. This will enable the development of a novel vaccine that ensures immunogenicity (especially neutralizing antibody induction) for the majority of the population vaccinated against COVID-19 (more than 100 million people in Japan) or previously infected with SARS-CoV-2 (more than 30 million people in Japan). Since it is not possible to study novel pandemics that have not yet occurred, we will develop and evaluate a vaccine against H7N9 influenza virus infection, which is considered to have immunogenicity limitations with current split vaccines, as a model infectious disease to evaluate the utility of this vaccine platform. However, the concept of this study can be applied to various infectious diseases other than novel pandemics (e.g., rabies, which requires rapid induction of neutralizing antibodies after exposure to pathogens), and it is expected to become a vaccine platform with wide ranges of applications with the progress of future research.