Development of a novel SARS-CoV-2 vaccine based on a replication-incompetent virus

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Most vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including mRNA vaccines, viral vector vaccines, and recombinant protein vaccines, induce serum antibodies to block the function of the spike (S) protein that is essential for viral entry. However, the induction of mucosal immunity in the upper respiratory tract is insufficient with current vaccines. Here, to develop a vaccine that can elicit protective immune responses in mucosa, we propose a novel SARS-CoV-2 vaccine based on a replication-incompetent virus that can induce mucosal immunity through intranasal inoculation. Because the replication-incompetent virus does not express the viral proteins necessary for viral replication, this virus can express viral proteins important for protection against infection but cannot produce new infectious progeny. Therefore, a vaccine based on this replication-incompetent virus would be superior to current vaccines because it could induce not only humoral but also cellular immunity as effectively as live-attenuated vaccines (e.g., FluMist, an influenza vaccine based on a cold-adapted live-attenuated influenza virus). In addition, the risk of reversion to the wild-type virus with pathogenicity, which is a concern with live attenuated vaccines, is low. Local mucosal immunity can be induced through intranasal administration. As the replication-incompetent virus is not a viral vector vaccine, multiple inoculations (vaccinations) are feasible. In addition, it would likely induce immune responses against structural proteins other than the S protein. As innate immune responses can be activated after a single inoculation with the replication-incompetent virus, there is no need for adjuvants. In this study, to develop a replication-incompetent virus as a new type of vaccine against SARSCoV-2, we will examine its efficacy in animal models and perform preclinical and Phase I clinical studies to verify its effectiveness in humans. Since this vaccine is generated by reverse genetics, the S gene can easily be replaced with the S gene from other strains, which makes it possible to prepare a new seed virus quickly when a novel variant with different antigenic properties emerges. Once the replication-incompetent SARS-CoV-2 is proven to be effective in humans, the concept of using a replication-incompetent virus could be established as a new vaccine modality and applied to infectious diseases other than COVID-19.