Review of: "Unadjuvanted intranasal spike vaccine booster elicits robust protective mucosal immunity against sarbecoviruses"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The preprint is a high quality pre-clinical study.. It addresses the very important issue of effective immunity enhancement against rapidly emerging variants of SARS-CoV-2. The aim of the study is of high scientific and practical relevance.
One serious disadvantage of the currently available COVID-19 immunization regimens that require intramuscular administration of the vaccine is the absence or very weak mucosal immunity. Lack of mucosal protection allows the virus, despite systemic vaccine induced immunity, to start replicating in the nasal cavity and nasopharynx. Before the virus can be stopped by systemic post-vaccination immunity, it can cause mild to moderately severe disease. Thus, it can be said that the most effective vaccines currently available efficiently protect against death or severe COVID-19-related disease, but these vaccines are less protective against the milder form of the disease. However, even a mild form of the disease can cause severe post-COVID conditions. Therefore, triggering mucosal immunity that can suppress viral replication at sites of viral entry, such as the nasopharynx, is an extremely important task for next-generation vaccines.
Authors of the preprint addresses the issue in murine model by two vaccination strategies that trigger efficient systemic and mucosal immunity. Both strategies require animal priming with an intramuscular conventional vaccine and further immunity boosting with a nasal vaccine. Immunity boosting can be achieved either by nasal application of (1) a recombinant S-protein or (2) an S-protein encoding mRNA in a specific formulation. As a conventional vaccine, the authors used mRNA-lipid nanoparticles.
The study convincingly shows that both strategies effectively induce humoral and T-cell immunity, which together protect against lethal viral challenges. Moreover, protection can be cross-reactive: immunity developed against one SARS-CoV-2 virus can protect against another SARS-CoV-1 virus. This cross-reactivity of post-vaccination immunity indicates that vaccination against one variant of SARS-CoV-2 can still effectively protect against another variant of the rapidly evolving virus.
From a technical point of view, the research described in the preprint is excellent. The experimental data obtained in the paper fully support the conclusions drawn. The data are well presented in written and graphical form. The manuscript is logical and well written.
Overall, this study is an important step towards achieving much better immune protection against COVID-19 than has been achieved worldwide to date.