Scientific considerations regarding the protein subunit candidate vaccines against SARS-COV-2

Report to the Spanish Ministry of Health COVID-19 vaccines task force on behalf of the *ad-hoc* scientific expert group of the Spanish Agency for Medicines and Medical Devices (03-08-2020)

Introduction

There are two protein-based vaccines that are being developed by two well-stablished Companies: Sanofi-Pasteur and Novavax. Novavax candidate vaccine has entered into phase I clinical trial whereas Sanofi Pasteur is still on preclinical testing. The Spanish *ad-hoc* scientific expert group have had access to the materials provided by Novavax and Sanofi during meetings with the companies not related to regulatory purposes.

Novavax

Although Novavax has not any registered vaccine in the EU, it has a well-proven experience in developing recombinant protein nanoparticle vaccines such as an influenza vaccine adyuvanted with saponin-based Matrix-M[1] (Nanoflu), and a vaccine against respiratory syncytial virus[2]). The former is close to be licensed by FDA.

Their candidate vaccine, NVX-CoV2373, is based on same recombinant protein nanoparticle platform and Matrix-M adjuvant as NanoFlu and consist of a full-length spike protein stabilized in a prefusion conformation, produced in the established Sf9 insect cell expression, plus the adjuvant.

In animal models[3] NVX-coV2373 elicits high titters of anti-S IgG antibodies and neutralizing antibodies, particularly after a two-dose regimen, and it also induces $CD4^+$ and $CD8^+$ T-cell responses.

Phase I trial Novavax´s candidate vaccine is underway in 131 adults 18-59 years in a two-dose schedule.

Sanofi Pasteur

The Company use a full-length stabilized spike prefusion protein preS dTM plus one squalene-based adjuvant: AF03 or the GSK´s adjuvant AS03. The later was a constituent of the H1N1pdm09 pandemic vaccine, and has been widely used.

The spike is produced in a baculovirus expression system technology already used for the marketed Flublok seasonal influenza vaccine.

Expected phase I clinical trial with a one or two-doses scheduled for 4Q 2020.

Therefore, the Spanish ad-hoc scientific expert group on COVID-19 vaccines **recommends:**

There are not yet available results in humans for any of the two vaccines. Novavax vaccine, but not the one from Sanofi, has data in animal models (mice and baboon model). With this very limited set of data, it is very premature to foresee any advantage of one vaccine over the other and our expert group, so far, cannot make a definitive

[1] doi:10.1371/journal.pone.0006032
[2] DOI: 10.1056/NEJMoa1908380
[3] https://www.biorxiv.org/content/10.1101/2020.06.29.178509v1.full.pdf

recommendation on this issue. However, it should be mentioned that many currently available vaccines are based on proteins (using either proteins purified from virions or produced by rDNA technology) and contain an adjuvant. These vaccines generally have shown very high efficacy and a very good safety profile. Thus, it is expected that highly efficacious and safe vaccines are going to be obtained against COVID-19. In this regard, the approach taken by both Companies based on developing adyuvanted vaccines containing a recombinant spike protein would most likely result in two efficacious and safe vaccines. Moreover, the previous expertise in vaccine development of Novavax and Sanofi Pasteur is a guarantee of success in developing their corresponding SARS-Co-V-2 vaccine. Sanofi´s adjuvant AS03 was widely use during 2009 H1N1 influenza pandemic and showed a good safety profile (the hypothetical association of the adjuvant with narcolepsy in adolescents vaccinated has never been fully demonstrated although with a very low risk, in some northern countries, there was an association).[4] The adjuvant to be include in the Novavax vaccine, although not as widely used as the AS03 adjuvant, has not been linked to any severe adverse event. Thus, both adjuvants are considered adequate to be included in the respective vaccines.

[4] https://doi.org/10.1016/j.vaccine.2018.08.008