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## Recombinant protein vaccines against SARS-CoV-2



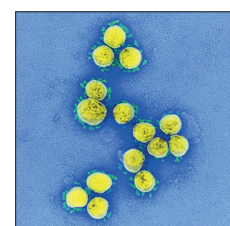
The development of vaccines against SARS-CoV-2 has proceeded at an unprecedented pace, resulting in emergency use approvals and accelerated deployment of multiple vaccines. This development and deployment has occurred within a year of the Public Health Emergency of International Concern declaration by WHO. However, some attempts to develop vaccines have run into difficulties in early clinical development.

Paul Goepfert and colleagues<sup>1</sup> describe clinical studies of CoV2 preS dTM, a stabilised pre-fusion spike protein vaccine produced in a baculovirus expression system administered alone or with one of two oil-in-water adjuvants (AS03 or AF03), in younger or older adults (299 aged 18–49 years and 142 aged ≥50 years). Alternate vaccination regimens were assessed including one or two doses and at different dose concentrations. After the trial commenced, it was discovered that a reagent used to quantitate the spike protein antigen cross-reacted with glycosylated baculovirus protein present in the formulation, resulting in an underestimate of antigen concentration of approximately four to six times, with either 1.3 µg (low dose) or 2.6 µg (high dose) administered. Immunogenicity was lower than expected, whereas reactogenicity was higher after the second dose of the adjuvanted vaccines. Some useful conclusions can be drawn from the study—for example, in individuals who are seronegative, an adjuvant is required, with AS03 resulting in greater immunogenicity than AF03. The higher dose with AS03 consistently resulted in the induction of neutralising antibodies in younger adults, although only 62.5% of those older than 60 years seroconverted for neutralising antibodies. The manufacturing process can now be optimised to achieve a higher antigen content and reduced host-cell protein contamination.

Keith Chappell and colleagues<sup>2</sup> also report a first-in-human trial of a recombinant SARS-CoV-2 spike glycoprotein stabilised in a pre-fusion conformation by a novel molecular clamp (spike glycoprotein-clamp [sclamp]) vaccine, produced in Chinese hamster ovary cells. The vaccine was administered to participants (120 aged 18–55 years) with a squalene-in-oil adjuvant, MF59, in alternate dose regimens, administering two doses of either 5 µg or 15 µg, and one or two doses of

45 µg. The vaccine was well tolerated in the young adult population, with induction of neutralising antibodies that were similar to amounts measured in recovered individuals after mild to moderate SARS-CoV-2 infection. However, care needs to be taken when comparing readouts across studies using neutralisation assays due to differences in assay design and the readout reported. The molecular clamp used in this vaccine design is derived from an HIV-1 peptide, and vaccination with the adjuvanted sclamp vaccine resulted in the induction of antibodies, which led to positive responses in some HIV screening tests. Although not a direct safety concern, this effect precludes further clinical development of the sclamp vaccine. Work is now underway to identify alternative trimerisation domains for a second-generation vaccine. Again, there were positive findings, with the study showing that a trimerised pre-fusion spike administered with MF59 adjuvant was safe and immunogenic in a small phase 1 clinical trial. Future work will be needed to explore the immunological differences across dosing regimens; two key immune modulators known to affect antibody responses were higher in the 5 µg and 15 µg but not the 45 µg regimen, albeit all two-dose regimens induced similar neutralising antibody titres.

It is not unusual for vaccine development programmes to encounter difficulties, or have a need to revisit the vaccine design or dosing regimen. Importantly, both of these trials have enabled the identification of those aspects of the vaccine composition or production process that require optimisation, enabling product development to resume. When the whole world requires vaccines against SARS-CoV-2, diversity in technologies used for production is beneficial, as the likelihood of a limited raw material resource negatively affecting vaccine supply will be reduced, and more existing manufacturing facilities could be brought into use. Although mRNA, adenoviral-vectored, nanoparticle, and inactivated vaccines are now in widespread use, booster doses will probably be required in the future to maintain immunity, particularly in older people in whom the immune response might be poorly coordinated, moving towards polarised and inflammatory states.<sup>3,4</sup> Recombinant protein vaccines are known to be effective at boosting pre-existing responses.<sup>5–7</sup>



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