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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 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 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 trimmerised 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-vector, 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. Recombinant protein vaccines are known to be effective at boosting pre-existing responses.
The difficulties ahead might therefore be reduced for these recombinant protein vaccines, which could have an important role in maintaining immunity against SARS-CoV-2. Future studies should include participants who are seropositive, either as a result of infection or previous vaccination, and use neutralising antibody assays standardised with an international reference standard, ideally testing the ability of serum to neutralise multiple SARS-CoV-2 variants of concern.

SCG is co-founder of Vaccitech (collaborators in the early development of the ChAdOx1 nCoV-19 vaccine) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines and a patent application covering ChAdOx1 nCoV-19. TL is named as an inventor on a patent application covering ChAdOx1 nCoV-19 vaccine) and named as an inventor on a patent covering use of ChAdOx1 nCoV-19 vaccine. SCG is co-founder of Vaccitech (collaborators in the early development of the ChAdOx1 nCoV-19 vaccine) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines and a patent application covering ChAdOx1 nCoV-19, and consultant to Vaccitech.

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Arterolane-based combinations for the treatment of uncomplicated falciparum malaria in Kenyan children

Antimalarial drug resistance is one of the various biological challenges putting malaria control strategies at risk1 in a time when the burden of malaria globally seems to be at a crossroads, with the situation no longer improving.2 Although there are currently no malaria parasites circulating in any corner of the world that could not be effectively treated with the existing registered antimalarials,3 the emergence and spread of resistance in parasites has, historically, been a problem in our fight against malaria. Therefore, it is reasonable that efforts are put towards the development of new antimalarials, and, in this respect, the antimalarial development pipeline appears as healthy and promising as it has ever been.4 However, it will still take a few years for the new generation of antimalarial drugs to be licensed and prequalified, so that they can be incorporated into malaria control strategies. In the meantime, rethinking our current use of antimalarials has become a potential exciting alternative in overcoming the threat of antimalarial resistance without having to wait for new drugs. Mimicking what is already routine practice in the fields of HIV or tuberculosis treatment, triple drug combinations as alternatives to artemisinin-based combination therapies (ACTs) are currently being explored for the treatment of malaria.5 Triple ACTs, comprising a fast-acting artemisinin derivative and two more slowly eliminated drugs (ideally with proven counteracting resistance mechanisms), should be efficacious and protect each individual drug of the combination from resistance. A large trial assessing two different triple ACTs (dihydroartemisinin-piperaquine-mefloquine and artemether-lumefantrine-amoquin) has shown the safety and efficacy of such an approach for the treatment of Plasmodium falciparum malaria, even in areas with artemisinin and ACT partner drug resistance.6

Synthetic peroxides, such as the ozonide arterolane maleate (OZ277), are among the most promising new antimalarials in development, and a fixed dose combination of arterolane-piperquine (Synriam) has already been licensed for use in India, with phase 3 trials in Africa and Asia showing excellent safety and efficacy results, both in adults7 and children,8 and for the treatment of P falciparum and Plasmodium vivax.9 Arterolane, however, had never been tested as part of a triple combination treatment. Therefore, Mainga Hamaluba and colleagues8 report the results of a single-centre, open-label, randomised, non-inferiority trial done in 217 Kenyan children (2–12 years old) in which arterolane-piperquine-mefloquine was compared with arterolane-piperquine and artemether-lumefantrine.

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