Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

group and 16 (0·1%) of 14 964 participants in the vaccine group had confirmed SARS-CoV-2 infection from day 21 after first vaccine dose (the primary outcome). A time-resolved plot of the incidence rate in the two groups showed that the immunity required to prevent disease arose within 18 days of the first dose. That protection applied to all age groups, including those older than 60 years, and the anecdotal case histories of those vaccinated but infected suggest that the severity of disease decreases as immunity develops. Three fatalities occurred in the vaccine group in individuals with extensive comorbidities, and were deemed unrelated to the vaccine. No serious adverse events considered related to the vaccine were recorded, but serious adverse events unrelated to the vaccine were reported in 45 participants from the vaccine group and 23 participants from the placebo group. Vaccine efficacy, based on the numbers of confirmed COVID-19 cases from 21 days after the first dose of vaccine, is reported as 91·6% (95% CI 85·6–95·2), and the suggested lessening of disease severity after one dose is particularly encouraging for current dose-sparing strategies.

The development of the Sputnik V vaccine has been criticised for unseemly haste, corner cutting, and an absence of transparency.[11] But the outcome reported here is clear and the scientific principle of vaccination is demonstrated, which means another vaccine can now join the fight to reduce the incidence of COVID-19.

We declare no competing interests.

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Next-generation COVID-19 vaccines: here come the proteins

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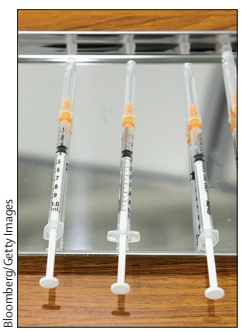
Since publication in January, 2020, of genomic information about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] many efforts have been made around the world to develop a vaccine against this virus. Three vaccines with more than 90% efficacy are licensed and beginning roll-out in some countries as of January, 2021,[2–4] which is a true feat of scientific endeavour and international efforts. However, SARS-CoV-2 continues to be a major threat worldwide and development of new COVID-19 vaccines remains essential.

In *The Lancet*, Peter Richmond and colleagues[5] report their phase 1, first-in-human, dose-finding and adjuvant justification study testing a stabilised trimeric spike subunit protein vaccine (SCB-2019). This vaccine differs from those already approved as it uses a stabilised protein trimer as the antigen. The researchers used Trimer-Tag, a protein derived from the C-terminus of human type I procollagen,[6] which preserves the trimeric conformation of the SARS-CoV-2 spike protein and has not previously been used in clinical trials. Trimer-Tag technology provides an alternative trimer stabilisation strategy to the molecular clamp derived from HIV proteins.[7] A phase 1 clinical trial of a SARS-CoV-2 vaccine (NCT04495933) was halted in December, 2020, because



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the molecular clamp induced antibodies recognised by HIV tests in trial participants after inoculation. Trimer-Tag vaccines are unlikely to encounter a similar issue.

The current trial tested three doses of protein (3 µg, 9 µg, or 30 µg) alone or with a fixed dose of either AS03, an oil-in-water adjuvant, or the TLR9 agonist CpG combined with Alum (CpG/Alum).[5] The vaccine requires a two-dose regimen, similar to currently approved vaccines, given at an interval of 21 days. The liquid vaccine formulation is stable for at least 6 months at a temperature of 2–8°C, which is an important added advantage as we attempt to immunise people in challenging environments all over the world. The primary objective of the study was to assess the safety and reactogenicity of the vaccine in healthy adults grouped by age (younger adults aged 18–54 years and older adults aged 55–75 years). 148 of 151 enrolled participants were included in the current analysis, of whom 64 (42%) were men and 87 (58%) women. The vaccine was well tolerated; most local adverse events were mild injection-site pain. Local events were more frequent with SCB-2019 formulations containing AS03 adjuvant (44–69%) than with those containing CpG/Alum adjuvant (6–44%) or no adjuvant (3–13%). Two grade 3 solicited adverse events were reported (pain after 9 µg dose of AS03-adjuvanted SCB-2019 and CpG/Alum-adjuvanted SCB-2019). Tolerability of the vaccine compares favourably with vaccines already approved.[8–10]

Although immunogenicity data were restricted to humoral responses in the study,[5] Richmond and colleagues noted that SCB-2019 alone (no adjuvant) was poorly immunogenic, but neutralising antibodies were recorded after the first injection with the higher doses (9 µg and 30 µg) of AS03-adjuvanted vaccine, which persisted for the remainder of the interim analysis period, with little meaningful difference between younger and older adults (all participants showed seroconversion). Furthermore, the magnitude of neutralising antibody titre and the ratio to binding antibodies was favourable compared with mRNA-based vaccines with reported efficacy.

A strength of this study is incorporation of the National Institute for Biological Standards and Control 20/130 reference (convalescent serum from a donor with standardised Ig and levels) bolstered by serum samples from convalescent patients who were either hospitalised with COVID-19 or required only outpatient treatment. Incorporation of reference standards is absolutely imperative for SARS-CoV-2 vaccine clinical trials moving forward, because of variability in binding and neutralising antibody assays between different organisations.[11] The Coalition for Epidemic Preparedness Innovations is also now offering testing of preclinical to phase 2 COVID-19 vaccine trial samples to harmonise assessment and enable comparison of candidates.[12]

One major drawback of the study by Richmond and colleagues is the absence of diversity among the 151 trial participants, of whom 132 (87%) were white,[5] which does not reflect the demographics of the global population to which this vaccine might one day be administered. Another potential concern is the flexibility and sluggish development of protein vaccines relative to existing authorised nucleic acid modalities (this phase 1 trial is only just complete when mRNA COVID-19 vaccines, for example, are already approved). Difficulties in tweaking and producing new protein vaccines in the landscape of emerging mutations that might escape from or lessen the efficacy of first-generation vaccines could be a severe drawback. However, the future of COVID-19 vaccines lies in promising vaccine candidates, such as this one, that have either equivalence or advantages in efficacy, stability, scalability, or cost.

AKB and PFM hold shares in VacEquity Global Health, a not-for-profit company that aims to develop a COVID-19 vaccine based on self-amplifying RNA technology; and hold shares in VaxEquity, a for-profit company that aims to develop self-amplifying RNA vaccines for pathogens other than SARS-CoV-2.

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Cabozantinib: a new first-line option for papillary renal cell carcinoma?

Papillary renal cell carcinoma (PRCC) is the most frequent subtype of non-clear-cell renal cell carcinoma (RCC);[1] however, it remains a rare and heterogeneous malignancy. PRCC is divided into type 1 and type 2, on the basis of different histological, molecular, and prognostic features.[2] Alterations in the MET pathway are frequent in PRCC, mostly observed in type 1 tumours (80%), but have also been described in up to half of type 2 tumours.[2,3]

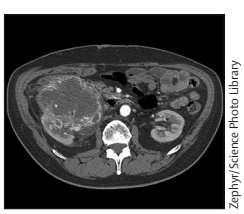
Because of the scarcity of high-level evidence, the appropriate management of patients with metastatic PRCC has not been clearly determined. Several issues are pending. First, PRCC has long been grouped together with non-clear-cell RCC subtypes, which have been further identified as very different clinical and genomic entities.[1] Second, because it is a rare entity, prospective clinical trials dedicated to PRCC had to deal with a slow accrual rate, especially when the population was selected on the basis of a specific molecular alteration.

Academic efforts from cooperative groups allowed the conduct of some clinical trials dedicated to advanced PRCC, mostly phase 2, single-arm, prospective trials in small cohorts. The SUPAP[4] and RAPTOR[5] trials showed low activity of either sunitinib or everolimus in patients with metastatic PRCC. Nevertheless, sunitinib has been considered the standard of care for PRCC,[6] partly based on extrapolated data from trials in patients with clear-cell RCC. In 2020, the AXIPAP trial reported encouraging activity of axitinib in 44 patients with metastatic PRCC (overall response rate [ORR] 28·6%), but did not lead to practice change.[7] These trials included a central expert pathological review before inclusion, which highlighted the need for such a procedure because 9–22% of tumours were misclassified by local review.

Retrospective data suggest evidence of anti-tumour activity of cabozantinib (targeting the vascular endothelial growth factor [VEGF] receptor and MET) in non-clear-cell RCC, specifically in the PRCC subgroup (ORR 27%),[8] but no prospective data are available yet.

The MET pathway has been identified as a promising target in PRCC. MET inhibitors, such as foretinib, savolitinib, and crizotinib, have been evaluated in several phase 2 studies, with promising results in *MET*-driven metastatic PRCC (ORR 18% to 50%), whereas no meaningful activity was observed in *MET*-independent tumours.[9–11] The SAVOIR phase 3 trial was the first attempt to compare the efficacy of savolitinib with that of sunitinib in patients with *MET*-driven PRCC. However, the study was closed prematurely, preventing any definitive conclusion to be reached on the potential benefit of selective MET inhibition in this setting.[12]

In this context of high unmet medical need, in *The Lancet*, Sumanta Pal and colleagues report the results of a randomised, open-label, phase 2 trial in patients with metastatic PRCC who were naive to treatment with VEGF-targeted or MET-targeted agents.[13] This academic study, done through a combined effort of North American cooperative groups, was initially designed as a four-arm study. The study enrolled 147 eligible patients confirmed to have advanced or metastatic PRCC after local histological review, who were allocated to either sunitinib (46 patients), cabozantinib (44 patients), savolitinib (29 patients), or crizotinib (28 patients). Allocation was stratified by previous therapy (ten [7%] patients received up to one



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