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.

Therapeutics, which are early stage biopharmaceutical companies involved in preclinical or early clinical development of immuno-oncology agents unrelated to the topic of this Comment, and have received research funding from Agilent and from Bristol-Myers Squibb through Stand Up to Cancer.

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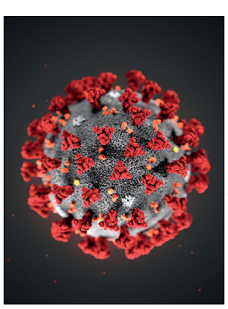
The starting line for COVID-19 vaccine development

Developing a safe and effective COVID-19 vaccine is a global priority to end this pandemic. In their dose-escalation, single-centre, open-label, phase 1 trial published in *The Lancet*, Feng-Cai Zhu and colleagues[1] report the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine, which expresses the full length spike glycoprotein of the Wuhan-Hu-1 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). 108 healthy adults who had not been exposed to SARS-CoV-2, aged between 18 and 60 years (mean age 36·3 years, 49% female), were sequentially enrolled to receive the low, middle, or high dose of the vaccine, given as an intramuscular injection, and observed for 28 days. At around 14 days, neutralising antibodies were detectable with live virus or pseudovirus neutralisation assays, in addition to binding antibodies (to receptor binding domain, spike glycoprotein) measured by ELISA. Dose-dependent antibody responses peaked at 28 days, with seroconversion (>four-fold increase in neutralising antibody titre) documented in 50–75% of participants in the middle and high dose groups. Further, specific T-cell responses toward the spike glycoprotein were shown by interferon (IFN) γ enzyme-linked immunospot, and flow-cytometry (assessing $CD4^+$ and $CD8^+$, IFNγ, tumour necrosis factor α, interleukin-2). Dose-dependent responses were detectable starting from 14 days in 83–97% of participants. The most commonly reported systemic adverse reactions were fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]), which were generally mild to moderate in severity, although more frequent in the high dose group.

Notably, high pre-existing Ad5 neutralising antibody titres (>1:200, in 44–56% of participants) were shown to compromise seroconversion, and attenuate peak T-cell responses, although vector-related febrile reactions were less frequent. Older participants (45–60 years) were found to have significantly lower humoral responses. This is one of the first-in-human trials of a COVID-19 vaccine candidate showing immunogenicity.

Two key questions are whether responses are sustained over time and whether they correlate with clinical protection after exposure to a circulating strain of SARS-CoV-2. Data from primate models suggest that measurable neutralising antibodies and specific T-cell responses could be associated with protection against virus challenge in vaccination or reinfection studies.[2,3] Further research, however, is necessary to evaluate safety, clinical efficacy, and duration of protection. A phase 2 study of this experimental vaccine (middle or low dose) has begun in China (NCT04341389) and Canada has approved an early phase human trial (NCT04398147). Other vaccine candidates are in rapid development. They are mostly based on the spike glycoprotein or its receptor binding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Published Online
May 28, 2020
https://doi.org/10.1016/
S0140-6736(20)31239-3

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domain because of better immunogenic and protective potential, but using different antigen delivery platforms (eg, recombinant protein or replicating or non-replicating viral-vector based vaccines, and DNA or mRNA vaccines); several are entering phase 1 clinical trials, or pending results.[4,5] Looking forward, other than immunogenicity, future trial design to establish efficacy will need to define the target groups (eg, health-care workers, individuals at high risk of severe illness), clinical endpoints (eg, reduction in virologically confirmed clinical illness, hospitalisations, deaths), optimal duration of observation (eg, virus exposure, side-effects, antibody titre change), and to anticipate antigenic change over time.

Results of this study indicate that some host factors might affect vaccine response. Suboptimal immunogenicity was reported among older participants, echoing the challenge seen with influenza vaccination. Further study in the older age group and the inclusion of individuals with underlying conditions are important, as they are at risk of severe disease and might benefit most from vaccine prevention. Pre-existing immunity against the Ad5 vector could compromise immunogenicity, potentially limiting effectiveness in populations in which the virus is endemic. The reported high seroprevalence (around 30–80%) in many countries had posed substantial challenges in vector-based vaccine development for other infections (eg, Ebola virus, HIV).[6-8] Whether using a rarer serotype or non-human primate adenovirus, adjuvants, booster or higher dose regimens, or other delivery platforms (eg, replication-defective vaccinia) could achieve greater degrees of immunogenicity is unknown and more research is needed.[4-6] Another general concern is the possibility of antibody-dependent enhancement (eg, non-neutralising antibodies, Fc γ-receptors) and increased cellular immunopathology (eg, T-helper-2 or T-helper-17 cell) in individuals who have been vaccinated if they are subsequently infected by a circulating SARS-CoV-2 strain, as suggested in preclinical studies of SARS-CoV-1 and Middle East respiratory syndrome coronavirus vaccines with whole-length spike glycoprotein (leading to research on a receptor binding domain-focused vaccine).[9-11] Animal studies can be considered to assess the potential risk of SARS-CoV-2 vaccine candidates.[5] Pre-existing, non-spike-specific T-cell responses from endemic human coronavirus exposure (eg, OC43, NL63) that cross-react with SARS-CoV-2 could further add to the complexity in predicting vaccine response and safety.[12,13] These concerns will need to be addressed in future clinical studies with close monitoring and regulatory review. Amid these uncertainties, this report of an immunogenic, tolerable vaccine candidate is encouraging at the starting line for COVID-19 vaccine development. Vaccine candidates shown to be efficacious will require substantial, well directed, and globally coordinated investments in production and delivery for their benefit to be realised.

NL reports non-financial travel and meeting support from Shionogi, consultancy fees and non-financial travel support from Janssen Pharmaceuticals, consultancy fees from hVIVO, consultancy fees and educational programme speaker support from Seqirus, consultancy fees and non-financial travel support from F Hoffmann–La Roche, consultancy fees and non-financial travel support from Sanofi-Pasteur, consultancy fees from Gilead Sciences, educational programme speaker and travel support from Genentech, and consultancy fees from CIDARA, outside the area of work commented on here. AM declares no competing interests.

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