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.

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Perspective

A short discussion about the SARS-CoV-2 mRNA-1273 vaccine

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ABSTRACT

The COVID-19 global pandemic has prompted accelerated vaccine development efforts. This perspective discusses the importance of SARS-CoV-2 vaccine candidates' recruitment of cellular T-cell immunity and encourages industry to increasingly investigate and publish parameters related to cellular immunity in their research reports.

To the Editor,

SARS-CoV-2 has caused a global health crisis that is second in severity to the 1918 influenza pandemic (Taubenberger and Morens, 2006). Development efforts to contain its wildfire-like spread with a safe and effective vaccine are of dire necessity and have called for immediate action. While success with one or more of the vaccine candidates is assumed and anxiously anticipated, it is not guaranteed due to compressed development timelines, the likely lack of results from long-term testing, the inchoateness of knowledge regarding betacoronavirus immunology, and the correctness of current vaccine strategies, most of which are based on presentation of the mutation-prone Spike protein with the reported potential to lead to exacerbation of disease through antibody dependent enhancement (ADE). Moreover, all vaccine candidates against Middle East respiratory syndrome coronavirus (MERS-CoV) have so far been unsuccessful, despite considerable expenditure of effort and money, especially in Saudi Arabia for the protection of commercially valuable camels and horses (Moore and Klasse, 2020).

Much depends on the rapid availability of a SARS-CoV-2 vaccine from a public health perspective; therefore, the slow and steady pace of conventional vaccine trials has been accelerated at "Warp Speed" (Funk et al., 2020) (in reference to the eponymously named US government vaccine program), potentially to the detriment of efficacy. This justifies an even closer look at published clinical trial data of front-line vaccine candidates such as Moderna's 1273-mRNA (as well as any other vaccine candidates in development).

On this basis, we carefully reviewed the recent report by Jackson et al., published in the *New England Journal of Medicine* (Jackson et al., 2020), disclosing preliminary results about the mRNA-based vaccine candidate from Moderna. Of particular interest, given the likely importance of T-cell immunity to vaccination against SARS-COV-2 from the killing of virus-infected cells and the production of cytokines, was a paragraph entitled, "SARS-COV-2 T-CELL RESPONSES" in the Results section. On the basis of intracellular cytokine staining (ICS), the authors state that the anti-COVID vaccine, mRNA-1273, "elicited CD4 T-cell responses that on stimulation by S-specific peptide pools were strongly biased toward expression of Th1 cytokines (tumor necrosis factor α > interleukin 2 > interferon γ), with minimal type 2 helper T-cell (Th2) cytokine expression (interleukin 4 and interleukin 13). CD8 T-cell responses to S-2P were detected at low levels after the second vaccination in the 100-μg dose group".

Here are a few caveats and interpretive qualifications of the above paragraph:

1 The ICS analysis involved cultivation of T-cells with supra-physiological concentrations of Spike peptide, thereby bypassing the normal antigen processing and presentation pathways that naturally operate *in vivo*. Hence, it is unknown whether or *even if* these Th1-like cells are predictive of vaccine-induced protection.
2 The question of whether CD4+ activation leads to a post-vaccination increase of $CD4^+$ memory T-cells is not addressed, despite its potential importance, since the goal of this (or any) vaccine is the induction and maintenance of long-lived protective immunity. A study featuring non-human primates evaluated the presence of memory T-cells (Corbett et al., 2020);

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similar data from human participants would still be of interest to the public. The identification of cell surface markers, such as CD45RO and CD45RA, may permit a more detailed analysis of the memory and secondary effector potential of these CD4+ cells.

3 The reported potential for Spike protein antibodies to induce ADE was also not addressed, in which IgG Fc domains of infection bind to Fc receptors (FcRs) on monocytic phagocytes to facilitate viral entry and replication.

4 The effect of the vaccine on anergic or exhausted T-cells was not evaluated, which is relevant for most at-risk elderly and immunocompromised patients, where lymphopenia and anergized T-cells have been described as markers of COVID-19 severity (Huang et al., 2020).

5 Given the ineffective endosome-to-cytosol translocation (Pardi et al., 2018), which has been described with mRNA vaccines, it is possible that the reduced CD8+ T-cell responses described in the manuscript were due to low MHC class I peptide loading efficiency.

Recent reports of SARS-CoV-2 vaccine candidates have included parameters of cellular T-cell immunity showing varying results. Pfizer and BioNtech have reported antibody and T-cell responses after vaccination with the vaccine BNT162b1 from a non-randomized open-label phase I/II trial (Sahin et al., 2020).

It is impossible to understate the economic and societal importance of a safe and effective SARS-CoV-2 vaccine and, accordingly, the rapid roll-out of mRNA-1273 (and other advanced stage vaccine candidates) has been met with cautious optimism. Ultimately, however, only the results of large-scale Phase 3 trials will determine whether, in fact, this optimism is justified.

Conflict of interest

The authors have no conflicts to disclose.

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