



T cell-oriented strategies for controlling the COVID-19 pandemic

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COVID-19 vaccination programmes are ongoing worldwide. Neutralizing antibodies are thought to be key for host protection against COVID-19; however, strategies that focus only on neutralizing antibodies may not be sufficient to cope with the pandemic in the longer term owing to the decay of antibody titres and the emergence of antibody-escape variants of SARS-CoV-2. Here, we describe the protective roles of T cells in COVID-19 and the conservation of T cell epitopes in SARS-CoV-2 variants of concern, and discuss the potential contribution of T cell-oriented strategies to controlling the COVID-19 pandemic.

COVID-19 vaccines induce both virus-specific antibodies and T cell responses, but it is the neutralizing antibodies (nAbs) that interfere with the entry of SARS-CoV-2 into host cells that are considered to be key for host protection. However, the level of nAbs declines with time after SARS-CoV-2 infection or vaccination¹. Moreover, recently emerging SARS-CoV-2 variants can escape nAbs elicited by natural infection or vaccination².

During a typical virus infection, CD4⁺ and CD8⁺ T cells contribute to controlling the virus by producing effector cytokines, such as IFN γ and TNF, and by exerting cytotoxic activity against virus-infected cells. Indeed, early and robust SARS-CoV-2-specific T cell responses have been associated with limiting the severity of COVID-19 (REF.³). In a study examining SARS-CoV-2-specific immune responses in patients with acute COVID-19, there was a strong inverse correlation between the frequency of SARS-CoV-2-specific IFN γ -producing CD8⁺ T cells and disease severity³. In addition, CD8⁺ T cells specific for conserved epitopes across common cold coronaviruses (CCoVs) are enriched in patients with mild COVID-19 (REF.⁴). Given that individuals not exposed to SARS-CoV-2 have cross-reactive T cells primed by previous CCoV infection, this suggests that pre-existing T cell immunity could ameliorate progression to severe COVID-19.

Intriguingly, host protection mediated by T cells has been observed in patients with COVID-19 who have insufficient humoral immune responses. Among patients with a haematological malignancy who became infected with SARS-CoV-2, anti-CD20 therapy was not associated with increased fatality, disease severity or viral load, despite low titres of SARS-CoV-2-specific IgG⁵. In these patients, including those receiving anti-CD20 therapy, SARS-CoV-2-specific T cell responses were detected, and higher levels of CD8⁺ T cell-mediated immunity were associated with improved patient survival.

Similarly, the protective roles of T cell-mediated immunity against SARS-CoV-2 have been demonstrated in animal models. Mice immunized with a vaccine expressing SARS-CoV-2 T cell epitopes exhibited decreased viral titres and reduced lung pathology when challenged with SARS-CoV-2, despite the absence of nAbs, which indicates that SARS-CoV-2-specific T cell vaccination confers partial protection from severe disease⁶. In a macaque model, CD8⁺ T cell depletion in convalescent animals was shown to partially abrogate host protection against SARS-CoV-2 re-challenge⁷. Together, these results in human patients and animal models indicate that T cells have a host protective role during COVID-19, particularly when the humoral immune response is insufficient.

SARS-CoV-2 nAbs elicited by infection or vaccination might become insufficient for host protection owing to declining titres over time and/or the emergence of viral escape variants. Although the kinetics of nAb titres vary among COVID-19 convalescent individuals, more than half of these individuals have waning levels of nAbs after 6 months¹. Moreover, SARS-CoV-2 variants of concern (VOCs) that have emerged have resulted in considerably reduced activity of nAbs induced by previous infection or vaccination. Sera from convalescent individuals and vaccine recipients have significantly weakened neutralizing activities against the Beta (B.1.351) and Delta (B.1.617.2) variants of SARS-CoV-2 (REF.⁸). The emergence and rapid rise to global predominance of the Delta variant (C.37), remind us that VOCs are likely to continue to evolve and challenge existing vaccines that depend primarily on humoral immune responses.

Compared with nAbs, SARS-CoV-2-specific memory T cells are maintained for a relatively long time (TABLE 1). A recent study showed that SARS-CoV-2-specific memory CD4⁺ and CD8⁺ T cell responses are sustained

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<https://doi.org/10.1038/s41577-021-00625-9>

Table 1 | Neutralizing antibodies and memory T cells elicited by different COVID-19 vaccine strategies

Type of vaccine antigen(s)	Form of protective immunity	Clinical effects	Longevity	Escape by virus variants
Spike (S) protein or gene	Neutralizing antibodies that block viral entry into host cells	Protection from infection and from severe disease	Relatively short	Easily escaped by mutations in antibody-binding sites
Spike (S) protein or gene; other structural and non-structural viral proteins or genes, or T cell epitopes	CD4 ⁺ and CD8 ⁺ T cells that produce cytokines and kill infected cells	Protection from severe disease	Longer lasting	Much harder to escape because HLA-restricted T cell epitopes vary between individuals and are distributed widely across a protein

in COVID-19 convalescent individuals for 10 months regardless of disease severity⁸. The persistence of memory T cell responses to SARS-CoV for 17 years has been demonstrated⁹. Moreover, there is increasing evidence that SARS-CoV-2 VOCs rarely escape memory T cell responses elicited by SARS-CoV-2 infection or vaccination. One study showed that SARS-CoV-2-specific T cell reactivity in COVID-19 convalescent individuals and vaccine recipients is reduced by only 10–22% by virus variants, including the Alpha (B.1.1.7), Beta, Gamma (P.1) and Epsilon (B.1.429) variants¹⁰. By analysing amino acid sequences, it was shown that 93% and 97% of the CD4⁺ and CD8⁺ T cell epitopes, respectively, were conserved in these variants. In principle, it is more difficult for a virus to evade T cell responses than nAbs because multiple T cell epitopes are distributed across both structural and non-structural viral proteins, including internal virus components, whereas nAbs tend to target a restricted protein domain exposed on the virus surface — such as the spike (S) protein of SARS-CoV-2, which is targeted by the currently approved viral vector and mRNA vaccines for COVID-19.

Currently, other vaccines with multiple targets, not limited to the SARS-CoV-2 S protein, are under development that should induce broad T cell responses. For example, UB-612, a protein-based vaccine incorporating multiple CD4⁺ and CD8⁺ T cell epitopes selected from the matrix (M), S2 and nucleocapsid (N) proteins of SARS-CoV-2, is in a phase II/III clinical trial (NCT04683224). Using a DNA platform, GX-19N expressing S and N proteins (NCT04715997) and GLS-5310 expressing S and ORF3a proteins (NCT04673149) are in phase I/II trials. There are also adenovirus vector vaccines expressing S and N proteins in development, including hAd5-S-Fusion + N-ETSD (NCT04843722) and VXA-CoV2-1 (NCT04563702). Chimpanzee adenovirus and self-amplifying mRNA vector vaccines expressing S protein and additional T cell epitopes (NCT04776317) and a synthetic modified vaccinia Ankara viral vector vaccine encoding S and N proteins (NCT04977024) are under investigation. Peptide vaccines using CD4⁺ or CD8⁺ T cell epitopes are being developed (NCT04885361), particularly for adults with congenital or acquired humoral immune deficiency (NCT04954469).

It is not likely to be possible to achieve herd immunity against the current COVID-19 pandemic owing to the decay of nAb titres and the continuing emergence of escape variants. A practical goal may therefore be to reduce damage to public health by making COVID-19 a controllable disease, similar to influenza or the common cold, although the elderly and immunocompromised patients would still be at risk of severe disease. We therefore need to continue work on such vaccines that induce durable and broad protective T cell-mediated immunity against COVID-19.

In the meantime, we should continue current vaccination programmes using the approved COVID-19 vaccines, which are still partially effective against SARS-CoV-2 VOCs, particularly in the prevention of severe or lethal COVID-19. Furthermore, SARS-CoV-2 breakthrough infections seem to be characterized by mild illness, low viral load and reduced (but not negligible) transmission risk. We believe that T cells could provide a solid defence against COVID-19 secondary to the activity of nAbs. Thus, sophisticated T cell-oriented vaccine strategies should be considered to control the COVID-19 pandemic in the longer term.

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Acknowledgements

This work was funded by Samsung Science and Technology Foundation under project number SSTF-BA1402-51.