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## T cell immunity to SARS-CoV-2 following natural infection and vaccination

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### ABSTRACT

SARS-CoV-2 first emerged in the human population in late 2019 in Wuhan, China, and in a matter of months, spread across the globe resulting in the Coronavirus Disease 19 (COVID-19) pandemic and substantial economic fallout. SARS-CoV-2 is transmitted between humans via respiratory particles, with infection presenting a spectrum of clinical manifestations ranging from asymptomatic to respiratory failure with multiorgan dysfunction and death in severe cases. Prior experiences with human pathogenic coronaviruses and respiratory virus diseases in general have revealed an important role for cellular immunity in limiting disease severity. Here, we review some of the key mechanisms underlying cell-mediated immunity to respiratory viruses and summarize our current understanding of the functional capacity and role of SARS-CoV-2-specific T cells following natural infection and vaccination.

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### 1. Role of T cells in respiratory infection

Conventional T cells are phenotypically and functionally diverse and have a critical role in long-lasting protection conferred by immune memory. CD8<sup>+</sup> cytotoxic T lymphocytes (CTL) in the respiratory tract blunt virus replication by directly killing infected cells, and secrete antiviral cytokines including IFN- $\gamma$  and TNF- $\alpha$ . CD4<sup>+</sup> T helper cells convey a multiplicity of functions key to coordinating and regulating antiviral immunity. Through provision of soluble mediators and co-stimulation, CD4<sup>+</sup> T follicular helper (T<sub>FH</sub>) cells determine the development of high-affinity neutralizing antibodies and germinal center B cell differentiation into memory and long-lived antibody secreting cells (reviewed in Ref. [1,2]). CD4<sup>+</sup> T cells also promote CD8<sup>+</sup> T cell activation and the formation of memory cells via chemotactic recruitment and CD40-mediated “licensing” of dendritic cells (DC) ([3–6] and reviewed in Ref. [7]). Memory CD4<sup>+</sup> T cells in the lung facilitate early virus control through recruitment of immune effectors by T<sub>H</sub>1 cytokine-dependent and independent mechanisms [8–10]. Induced by infection, CD4<sup>+</sup> ThCTL in the lung exert MHC class-II restricted cytotoxicity and IFN- $\gamma$ -producing, cytotoxic CD4<sup>+</sup> T cells from circulation have been associated with protection to influenza in

humans [11,12]. Through a wide variety of effector mechanisms, virus-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells eliminate infected cells, control the inflammatory milieu, and facilitate the optimization of the humoral response.

Murine models are often used to demonstrate mechanisms of T cell-based protection from viral replication and disease. While mice are not a natural host for human coronaviruses (hCoV), passage or structure-guided viral adaptation, and careful host strain selection allow for the study of virus-mediated pathology [13,14]. In the absence of CD4<sup>+</sup> T and B cells, memory CD8<sup>+</sup> T cells elicited to an immunodominant epitope in the spike (S) protein produced multiple effector cytokines including IFN- $\gamma$ , TNF- $\alpha$ , IL-2, and granzyme B (GzmB), exhibited *in vivo* cytotoxicity, and reduced viral loads following lethal Severe Acute Respiratory Syndrome (SARS)-CoV challenge [15]. During primary SARS-CoV infection, CD4<sup>+</sup> T cells mediate virus control and impact disease progression. Aged BALB/c mice depleted of CD4<sup>+</sup> T cells experienced enhanced cytokine production and respiratory disease, delayed SARS-CoV clearance from the lungs, and reduced neutralizing antibody titers and pulmonary influx of lymphocytes [16]. Nucleocapsid (N)-specific airway memory CD4<sup>+</sup> T cells generated by intranasal vaccination efficiently protected against lethal disease through rapid production of IFN- $\gamma$ . Airway depletion of CD4<sup>+</sup> cells and IFN- $\gamma$  decreased survival and resulted in increased pathological changes in the lungs. Furthermore, airway CD4<sup>+</sup> T cell-derived IFN- $\gamma$  was required for optimal respiratory DC maturation and migration to the draining mediastinal lymph node. Finally, airway CD4<sup>+</sup> T cell derived

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IFN- $\gamma$  promoted CXCR3-dependent T cell mobilization to the lungs [17], consistent with models described for other viruses and sites of infection [18–20]. Taken together, murine studies of pathogenic coronavirus infection largely demonstrate a protective role for T cells and suggest that SARS-CoV-2-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells will control virus replication and moderate the pathology associated with COVID-19.

## 2. T cell responses to SARS-CoV-2

### 2.1. Specificity, phenotype, and function following infection

The significance of T cells in human immunity to SARS-CoV-2 may be inferred from case studies of COVID-19 patients with agammaglobulinemia. Although limited to only a few documented cases, COVID-19 patients with X-linked or autosomal recessive agammaglobulinemia were able to recover from infection without oxygen ventilation or intensive care, suggesting that while B cells and antibodies are critical for preventing infection or reducing inoculum size, T cell responses may be sufficient to clear infection with minimal disease [21,22].

Lymphopenia is commonly noted in COVID-19 patients, especially in severe cases [23–28], with some evidence of an inverse correlation between T cell abundance and disease severity [29–32] and age [30], and more pronounced decreases of CD8<sup>+</sup> T cells [26]. In mild cases, higher CD8<sup>+</sup>/CD4<sup>+</sup> T cell ratios were observed [33], whereas the opposite trend was found in severe cases [23,26]. Elevated neutrophil/T cell ratios were also found in severe COVID-19 samples compared to healthy donors, moderate, and recovered cases, and were positively correlated with higher Acute Physiology And Chronic Health Evaluation (APACHE) III scores. In the aged ( $\geq 65$ ), a scarcity of naïve T cells, coupled with virus-induced lymphopenia has been strongly associated with poor disease outcomes, possibly contributing to delayed and/or uncoordinated adaptive immune responses [34]. Collectively, these observations indicate that differences in peripheral blood immune cell composition may be prognostic of severe COVID-19 [32,35]. The clinical relevance of lower T cell counts in circulation across disease states remains unclear however, and may in part reflect margination or recruitment and sequestration of activated cells in lung tissue to combat infection [36,37], activation-induced cell death in lymphoid organs [38], and/or dysregulation of antigen presenting cells [39,40].

Several studies using IFN- $\gamma$  enzyme-linked immunosorbent spot (ELISpot), intracellular cytokine staining (ICS), and/or activation-induced marker (AIM) assays have demonstrated that CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses to SARS-CoV-2 are readily detectable (80–100% and 70–80%, respectively) in the majority of PBMCs from adult COVID-19 patient samples ranging in disease severity. Broad specificity to structural and non-structural proteins (NSPs) was found, and immunodominance was generally associated with protein abundance [23,34,41–47]. For both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, responses to S, membrane (M), and N structural and accessory proteins appear dominant, with subdominant responses to ORF 1 ab-encoded NSPs. Based on varying results however, how T cell specificity, magnitude, and kinetics relate to disease severity is not yet fully understood [33,45,48].

Pre-existing, cross-reactive T cells have the capacity for accelerating virus clearance with improved clinical outcomes following infection [49]. Thus, tremendous interest in the potential for T cell cross-reactivity between human circulating “common cold” coronaviruses (OC43, HKU1, NL63, and 229E) and SARS-CoV-2 has been explored. Reactivity to SARS-CoV-2 S and non-S peptide pools has been found in 20–50% of unexposed donors from across the globe, albeit of lower magnitude compared to COVID-19 samples and predominantly within the CD4<sup>+</sup> compartment [23,31,42,44,50–52].

In one study, a high degree of epitope homology (~67%) between SARS-CoV-2 and other hCoVs resulted in cross-reactivity in 57% of cases (21/37) [52]. In another study, S-specific responses in individuals not exposed to SARS-CoV-2 were largely derived from the C-terminus in the S2 subcomponent or stem region, which has higher homology to endemic hCoVs [44]. T cells to SARS-CoV have been detected in humans more than 10 years after infection, demonstrating the capacity for generating virus-specific memory T cells that theoretically could be recruited into the SARS-CoV-2 response following infection [47,53]. Responses to a NSP7 epitope conserved in animal betacoronaviruses have also been described, suggesting additional sources of cross-reactivity [47]. Cross-reactive T cells have not been identified in all studies, however; Peng et al. [33] found no evidence of cross-reactivity in SARS-CoV-2-naïve subjects, possibly reflecting differences in experimental conditions, prevalence of particular HLA genotypes, and exposure history to hCoVs. Prospective studies comparing the antiviral response to SARS-CoV-2 in individuals with and without cross-reactive memory cells would potentially clarify the implications of pre-existing immunity on pathogenesis.

Early retrospective and cross-sectional studies to evaluate the contribution of cross-reactive memory and *de novo* SARS-CoV-2 T cell responses to protection have characterized the phenotype, functional capacity, and activation status of T cells in acute and convalescent COVID-19 patient samples (reviewed in Ref. [54–56]). SARS-CoV-2-reactive T cells can acquire a variety of memory phenotypes, indicating their potential for self-renewal as long-lived memory cells in lymphoid and peripheral tissues. The majority of current data suggests that although both T cell subsets can acquire central memory (T<sub>CM</sub>), effector memory (T<sub>EM</sub>), and stem cell-like memory (T<sub>SCM</sub>) phenotypes, there is a CD4<sup>+</sup> T cell bias towards T<sub>CM</sub>, and CD8<sup>+</sup> T cells towards T<sub>EM</sub>, with heterogeneity in differentiation status [23,26,31,33,45,52,57,58]. In studies of mild to severe COVID-19 [31,57,58], CD8<sup>+</sup> T<sub>EM/TEMRA</sub> cells appeared to be less differentiated compared to critical cases, including those with acute respiratory distress syndrome (ARDS) [23,45]. Studies directly comparing different stages of infection and recovery across the disease spectrum would inform understanding of the elicitation, phenotype, kinetics, and longevity of SARS-CoV-2-specific T cells, and importantly, how they might influence the response to reinfection.

Both T cell hyperactivation and exhaustion have been described in COVID-19. T cells with an activated phenotype, including increased expression of CD38, CD39, HLA-DR, Ki-67, and CD69 have been reported in acute and convalescent samples [26,31,35,44,59], with one study correlating CD38 expression with disease severity [31]. Additionally, reports of IL-6 or GM-CSF producing CD4<sup>+</sup> T cells in the blood [60] and decreases in immunoregulatory subsets such as Treg, and  $\gamma\delta$  T cells have been described [61–63]. Conversely, increased inhibitory receptor expression on CD8<sup>+</sup> T cells including PD-1, TIM-3, TIGIT, CTLA-4, and NKG2A have also been reported early following infection, possibly reflecting some degree of immunosuppression and/or functional exhaustion, although upregulation of many of these markers may reflect cell activation [29–31]. Functional impairment may not uniformly impact memory responses in all recovered individuals. For example, decreases in inhibitory marker expression returned to baseline in one study [29] and anamnestic responses of memory cells from convalescent samples in another report showed antigen-specific cell proliferation and IFN- $\gamma$  and TNF cytokine production following restimulation *in vitro* [31]. Seemingly discordant findings related to T cell activation status, functional responsiveness, and duration highlight the highly heterogeneous nature of immune responses in COVID-19 patients.

More recently, deep profiling of COVID-19 samples have

revealed several “immunotypes” with differences in T cell activation status and phenotype, likely influenced by variations in immune response kinetics, disease severity, host genetics, and underlying co-morbidities. For example, an integrated study of ~250 immune and clinical features from healthy, recovered, and COVID-19 donors revealed three major signatures, which were associated with different health trajectories: 1) robust activation and proliferation of CD4<sup>+</sup> T cells, a relative lack of circulating T<sub>FH</sub> (cT<sub>FH</sub>), modest activation of EMRA-like cells, highly activated or exhausted CD8<sup>+</sup> T cells, and T-bet<sup>+</sup> plasmablasts 2) T-bet<sup>bright</sup> effector-like CD8<sup>+</sup> T cell responses, less robust CD4<sup>+</sup> T cell responses, and Ki-67<sup>+</sup> plasmablasts and memory B cells, and 3) lack of lymphocyte responses in ~20% of subjects, indistinguishable from healthy donors [26]. Of the three profiles, dimensionality reduction analyses found an association between immunotype 1 and increased disease, supporting the model of an exaggerated immune response and immunopathology. This is consistent with a separate study finding an association between early, elevated and sustained proinflammatory markers, viral load, and severe disease [32]. In accordance, 18/20 of the top parameters associated with severe disease were related to increased CD4<sup>+</sup> and CD8<sup>+</sup> T cell activation in a companion study [35]. Additionally, a reduction in the frequency of CD161<sup>++</sup> CD8<sup>+</sup> cells comprised of mostly mucosal-associated invariant T (MAIT) cells was found in the blood of severe COVID-19 patients, and was associated with higher APACHE III scores, possibly reflecting airway recruitment and potentiation of tissue inflammation [35,64]. While immune profiling studies can identify signatures that predict disease outcome, it is difficult to parse out determinants of protection or disease.

In contrast to dysregulated T cell signatures and associations with COVID-19, polyfunctional, CD4<sup>+</sup> T<sub>H1</sub>-biased or balanced T<sub>H1/2</sub>, T<sub>FH</sub>, and CTL responses have been associated with protective immune responses to viruses, including HIV and influenza [65]. Several studies have demonstrated the elicitation of CD4<sup>+</sup> T cells with a dominant (and sometimes polyfunctional) T<sub>H1</sub>-cytokine profile including production of IFN- $\gamma$ , TNF- $\alpha$ , and IL-2 in convalescent mild and severe COVID-19 patients [31,34,42,33]. Additionally, production of IFN- $\gamma$ , TNF- $\alpha$ , GzmB and/or surface expression of the CD107a marker of degranulation has been detected in CD8<sup>+</sup> T cells [31,33], with one report demonstrating higher levels of cytotoxicity markers in severe cases [66]. In contrast to mild cases [57] however, evidence of type 2 (IL-5, IL-13, IL-9, and IL-10) and type 3 (IL-17A, IL-17F, and IL-22) responses in more severe COVID-19 was found in some [23,31,32], but not in all reports [48]. These responses may contribute to the production of IL-1 $\beta$ , IL-6, CXCL8/IL-8, TNF, and CXCL10/IP-10, which are associated with inflammation, organ damage, T cell impairment, and neutrophilia [34,67,68]. Pathogenic inflammation in severe cases of COVID-19 has been associated with an increased risk of thrombosis and coagulopathy, and rare cases of multisystem inflammatory syndrome in children (MIS-C), which bear some resemblances to Kawasaki disease and toxic shock syndrome. Although the pathophysiology of MIS-C is still unclear, it has been speculated that autoantibodies, immune complexes, and/or antibody-dependent enhancement of cytokine release may be involved. Additionally, T cell recognition of virally-infected cells and/or self-antigens, and possible recognition of superantigen sequences may further contribute to vasculitis and tissue damage, including cardiac injury [56,69,70]. Notably however, distinct differences in the inflammatory response, T cell composition, IL-17A, and biomarkers associated with arterial damage between MIS-C, severe acute COVID-19, and Kawasaki disease have been reported, and a better understanding of mechanisms driving disease progression in patients of all ages is needed [71].

Virus-specific T<sub>FH</sub> are compulsory for the development of affinity-matured neutralizing antibodies. Phenotypic analyses of

CD4<sup>+</sup> T cells from COVID-19 patients have revealed the heterogeneity of circulating T<sub>FH</sub> (cT<sub>FH</sub>) (CXCR5<sup>+</sup> PD-1<sup>+</sup>) [26,31,34,35,48,51,57,59,72]. In convalescent mild to moderate COVID-19, although S-specific cT<sub>FH</sub> were enriched for T<sub>H17</sub>-like (CCR6<sup>+</sup>CXCR3<sup>-</sup>) cells, T<sub>H1/2</sub>-like (CCR6<sup>-</sup>CXCR3<sup>+/-</sup>) cells were associated with the highest plasma neutralizing activity [72]. Furthermore, high-dimensional cytometry analyses from mild, hospitalized, and recovered COVID-19 samples revealed an activated signature (ICOS<sup>+</sup> and/or CD38<sup>+</sup>), suggesting recent germinal center activity [26,57], although elevated plasma CXCL13 levels at later time points post-symptom onset have been associated with severe COVID-19 [32]. However, inverse correlations between total S-specific cT<sub>FH</sub> and the CCR6<sup>+</sup> CXCR3<sup>-</sup> T<sub>H17</sub>-like subset, and disease severity were found in acute and convalescent samples [34]. Interestingly, differences in antigen specificity have been found between CD4<sup>+</sup> cT<sub>FH</sub> and non-cT<sub>FH</sub>. For example, S-specific CD4<sup>+</sup> T cells were skewed towards a cT<sub>FH</sub> profile in mild and severe convalescent COVID-19 samples, whereas M and N specific CD4<sup>+</sup> T cells were skewed towards a T<sub>H1</sub> or T<sub>H1</sub>/T<sub>H17</sub> profile [31], consistent with a previous report demonstrating enriched cT<sub>FH</sub> reactivity to the influenza hemagglutinin surface protein relative to nucleoprotein [73]. Links between antigen specificity and effector function of CD4<sup>+</sup> T cells may reflect differences in viral antigen handling in lymphoid organs, with important implications for vaccine antigen/epitope inclusion. A limitation to the aforementioned studies however, was the inability to separately distinguish contributions between cT<sub>FH</sub> and Foxp3<sup>+</sup> T follicular regulatory (cT<sub>FR</sub>) cells potentially present in circulation, which are both CXCR5<sup>+</sup> PD-1<sup>+</sup> (reviewed in Ref. [74]).

In addition to immune profiling by flow cytometric techniques, RNA sequencing and multispectral imaging have provided additional insights into T cell heterogeneity and functional plasticity. In one study, transcriptomic analyses of peripheral SARS-CoV-2-reactive CD4<sup>+</sup> T cells identified a diminution of Treg and dominant expansion of ThCTL in severe COVID-19 illness. A distinct cT<sub>FH</sub> signature was also associated with dysfunction and cytotoxicity, possibly contributing to impaired humoral immune responses [75]. Similar to another study that found elevated chemokine levels associated with immune cell recruitment and survival in the plasma of severe patients [32], the CD4 ThCTL were highly enriched in expression of transcripts encoding chemokines involved in the recruitment of myeloid cells to sites of viral infection, possibly exacerbating pathogenic inflammation in COVID-19 [51]. In lymphoid tissues, imaging of spleens and lymph nodes from COVID-19 autopsy specimens revealed a defect in germinal center formation, including a lack of Bcl 6<sup>+</sup> T<sub>FH</sub> differentiation, accumulation of non-germinal center B cells, and aberrant TNF- $\alpha$  production from CD4<sup>+</sup> T<sub>H1</sub> cells [76]. Thus, while antiviral CD4<sup>+</sup> T<sub>H1</sub>, T<sub>FH</sub>, and ThCTL signatures are generally considered protective, dysregulation may contribute to immunopathology and/or defects in pathogen clearance. Further studies on the molecular and cellular elements governing SARS-CoV-2-specific CD4<sup>+</sup> T cell effector programs are warranted to reveal their relative beneficial and detrimental influences.

## 2.2. Vaccine-elicited T cell responses

Given the relatively high frequency and potential long-term consequences of severe COVID-19, the establishment of herd immunity to SARS-CoV-2 through vaccination is favored. Safe and effective SARS-CoV-2 vaccines are urgently needed for immunoprophylaxis and priming for rapid anamnestic responses to subsequent exposures. There are currently over 200 candidates worldwide in various stages of preclinical and human testing [77]. Correlates of immune protection to COVID-19 are unknown, but the



major goal of most vaccines is the induction of neutralizing antibodies due to their potential for protecting the lower airway and reducing disease severity. They may also reduce the duration of virus shedding in the upper airway and limit transmission. However, coordinated and lasting CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses with the proper specificity, phenotype, and function are also likely to be critical components, as multiple studies have reported that circulating antibodies to CoVs may be short-lived, or of low magnitude and/or potency [28,78,79]. Therefore, rapid expansion of vaccine-induced memory lymphocytes may be necessary to boost immunity and curtail COVID-19 disease and transmission.

Currently in phase III clinical trials in the U.S. is mRNA-1273. The vaccine was developed by NIAID and Moderna, and encodes the prefusion-stabilized S trimer encapsulated in lipid nanoparticles for intramuscular delivery. In a preclinical prime boost study in mice, 1.0 µg mRNA-1273 elicited a T<sub>H</sub>1-biased cytokine profile (IFN-γ, TNF-α, IL-2), a paucity of IL-4 and IL-5 producing T<sub>H</sub>2 cells, and CD8<sup>+</sup> T cells, demonstrating an immunological signature consistent with protection and unlikely to be associated with a vaccine-enhanced disease syndrome. T cell responses were accompanied by strong neutralizing activity, protection from mouse-adapted SARS-CoV-2 infection in the lung and nose, and no evidence of pulmonary immunopathology, even at sub-protective doses [80]. In rhesus macaques, T<sub>H</sub>1-biased responses to mRNA-1273 were also detected, in addition to antigen-dependent CD40L/CD154 upregulation and IL-21-producing peripheral T<sub>FH</sub>, with low or undetectable T<sub>H</sub>2 or CD8<sup>+</sup> T cells. Robust neutralizing activity was associated with rapid protection from viral replication and lung pathology [81]. In the phase I human trial, mRNA-1273 was well-tolerated, and induced CD4<sup>+</sup> T<sub>H</sub>1-biased (TNF-α>IL-2>IFN-γ) responses, little T<sub>H</sub>2 cytokine expression (IL-4 and IL-13), and detectable CD8<sup>+</sup> T cell responses after two immunizations with 100 µg in younger and older adults [82,92]. Furthermore, mRNA-1273 elicited neutralizing activity about 3-fold above the geometric mean titer of a panel of convalescent sera.

In a separate phase 1/2 study assessing the safety and immunogenicity of a lipid nanoparticle formulated mRNA vaccine encoding the trimeric receptor binding domain (RBD) of S, BNT162b1 (Pfizer and BioNTech) was also able to induce neutralizing antibodies 1.9–4.6-fold greater than a panel of convalescent human sera [83]. In a companion study [84], it was shown that two doses (1–50 µg) BNT162b1 induced CD4<sup>+</sup> T<sub>H</sub>1-biased and CD8<sup>+</sup> T cell responses, with little evidence of a T<sub>H</sub>2 (IL-4) response, indicating sufficient T cell help despite the possibility of fewer available epitopes compared to full-length S [52,72]. An alternative candidate (BNT162b2) encoding an optimized full-length S (similar to mRNA-1273) has been selected for advancement into upcoming phase 2/3 studies based on favorable safety, immunogenicity, and the increased probability to generate consistent responses across diverse populations and older adults due to a greater diversity of potential T cell epitopes [85]. Other nucleic acid delivery platforms have been explored; immunogenicity profiling of DNA candidates encoding different forms of S in four rhesus macaques 5 weeks following immunization detected IFN-γ producing CD4<sup>+</sup> and CD8<sup>+</sup> T cells, with little evidence of IL-4 production, suggesting a T<sub>H</sub>1-biased response [86].

Alternative delivery platforms of S include replication-deficient viral vectored vaccines and nanoparticles. An IM-delivered adenovirus type-5 (Ad5) vectored vaccine (CanSino) in China elicited T cell responses that peaked at 14 days, but were still detectable at day 28 in a phase I trial, although less of a dose effect was observed at the later timepoint. CD4<sup>+</sup> and CD8<sup>+</sup> T cells produced IFN-γ, TNF-α, and IL-2, with a large proportion of both T cell subsets being single IFN-γ producers [87]. In the UK, a phase 1/2 trial testing a chimpanzee adenovirus-vectored vaccine (ChAdOx1

nCoV-19/AZD1222, AstraZeneca) expressing codon-optimized S found T cell responses as early as day 7 that peaked at day 14, and were detectable out to day 56, the last collection timepoint in the study [88]. Unlike the antibody response however, cellular responses were similar between the one and two-dose groups based on IFN-γ ELISpots, but CD4 and CD8 responses were not separately measured. In a phase 1/2 study in Russia, S-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation and increased concentrations of IFN-γ were found following a rAd26 and rAd5 vector-based heterologous prime-boost regimen encoding full-length S (Gamaleya Research Institute), peaking at day 28 [89]. Finally, phase 1/2 trial results of a full-length S protein nanoparticle vaccine (NVX-CoV2373, Novavax) revealed a T<sub>H</sub>1-biased, polyfunctional CD4<sup>+</sup> T cell response on day 28, with Matrix-M1 adjuvant providing a dose sparing effect in the lower 5 µg dose group [90]. While encouraging, a caveat for interpreting phase 1–2 studies is the comparison of vaccine-elicited antibodies to those from convalescent serum since a level that correlates with protection is not yet known and each panel of convalescent sera is comprised of samples from subjects with different levels of disease severity. Nonetheless, data across several distinct vaccine platforms demonstrate favorable safety signals and immunogenicity of candidate vaccines that have been advanced into efficacy testing, with the latest developments reviewed in Ref. [77,91] and the WHO draft landscape of COVID-19 candidate vaccines.

### 3. Summary

In response to the devastation caused by the COVID-19 pandemic, scientists worldwide have inspired hope through expeditious research efforts in basic and translational avenues in unprecedented fashion. It is clear that T cells are elicited to multiple viral proteins following infection and that T cells possessing antiviral signatures associated with safety and protection and can be achieved by vaccination. As observational/longitudinal studies continue, the relationships between infection status, host immunity and disease trajectory will more clearly come into focus. Although T cell durability to SARS-CoV-2 remains to be determined, current data and past experience from human infection with other CoVs demonstrate the potential for persistence and the capacity to control viral replication and host disease, and importance in vaccine-induced protection.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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