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VIA Electronic Mail to: robert.califf@fda.hhs.gov, peter.marks@fda.hhs.gov

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Dear Dr. Califf and Dr. Marks:

We urge the FDA to include in its guidance to vaccine developers a recommendation for T-cell assessment in COVID-19 vaccine clinical trials to more comprehensively measure immune response. Measuring T-cell responses in addition to antibodies is critical to help better evaluate vaccine efficacy and inform decisions regarding ongoing protection against current and future variants.

Despite remarkable advances in detecting, treating, and preventing SARS-CoV-2 infection, the emergence of the Omicron variant was a striking reminder of how much there still is to learn about the immune response to this virus. To date, we lack a clear-cut correlate of protection for the SARS-CoV-2 vaccines and the assessment of the adaptive immune response to SARS-CoV-2 infection and vaccination has largely focused on antibodies (Abs), with much less emphasis on the T-cell response despite a likely role in protection from severe disease.

The limited study of T cells in SARS-CoV-2 research is impeding our ability to inform policies related to emerging variants and long-term immune protection after Ab titers have appropriately declined following infection and/or vaccination. The focus on Abs stems in part from the ease of their quantitative measurement, making them more convenient to include in research and clinical trials. Recent advances now enable comparable T-cell assessment with precision and at scale, and it is opportune to incorporate assessment of this other half of the adaptive immune system in vaccine trials and other research now.

As discussed below, if thorough data had been collected on the broader adaptive immune response – including Abs and T cells – since the beginning of the COVID-19 pandemic, we would better understand the risks posed by the emerging variants and could more readily provide swift messaging to counter misinformation and associated vaccine hesitancy. This gap was also highlighted in the initially announced results of the

BNT162b2 vaccine trial in a pediatric population ranging from ages 2 to under 5 years that were deemed insufficient to support emergency use authorization, yet only antibody results were considered in the analysis. Better understanding of correlates of protection, including the contribution of cellular immunity in the form of a T-cell response, may have informed decisions regarding potential authorization of the vaccines in this population.

Examining the T-cell response has applications for clinical diagnosis and management, evaluation of protective immunity, and vaccine assessment. Studying the broader adaptive immune response to COVID-19 may also help determine why some patients become critically ill while others are asymptomatic[1], which may help advance solutions to diagnose, treat and prevent the disease. As mounting research continues to demonstrate the importance of T cells in COVID-19, we urge including the study of cellular immunity broadly across research, and especially in discovery and development of new or modified vaccines.

Improving Information for Vulnerable Populations

There are ~7 million immunocompromised people living in the U.S. who struggle with how to protect themselves[2]. We are lacking data on the full adaptive immune response in these populations. Information about the T-cell response may help tailor vaccine schedules, use of prophylactic interventions, or other measures to address the increased risk of these populations.

With COVID-19 disproportionately impacting certain populations, we must utilize every tool at our disposal, including T-cell assessment, to fully understand immunity and address inequities worsened by the pandemic. Conducting this research and better understanding the role of T cells in protective immunity will provide more robust information about correlates of protection that will benefit our understanding for the entire population, but especially those who are most vulnerable.

Strengthening the Public Health Response & Public Confidence

It is important to note that there are two dimensions to protection: (1) the prevention of an individual being infected with SARS-CoV-2, and (2) if a person is infected, reducing the likelihood of severe illness and death. Studying the Ab response helps inform the first dimension, but the Delta and Omicron variants have highlighted the risk of an exclusive focus on Ab-based protection because of the potential of these variants to partially evade antibody responses.

However, with the emergence of the Omicron variant, a distinct discourse emerged: expert voices began pointing to the importance of T cells almost immediately, providing balance to concerns about the predicted loss of Ab-mediated protection. Multiple studies[3-7] have shown the preservation of vaccine-induced T-cell response against Omicron, likely contributing to continued vaccine efficacy in protecting against severe illness and death. This work must continue and be amplified by those informing policy and explaining the latest science to the lay public.

For example, one study[8] generated sensationalized national media headlines suggesting the ineffectiveness of the Johnson & Johnson vaccine against Delta. These findings were directly refuted by the company's study[9] that demonstrated "strong, persistent" protection, a conclusion supported by independent studies[10,11]. The first study only reported the Ab response, not the full nature of the immune response including T cells. *This type of misinformation can impair the public health effort to identify optimal vaccines, affect vaccine confidence, and exacerbate vaccine hesitancy, and could be avoided with research on the broader adaptive immune response, including T cells.*

Given the important and complementary roles of Abs and T cells, we cannot truly understand immunity by assessing only the humoral aspect of the adaptive immune response. For example, robust protection against hospitalization with SARS-CoV-2 Omicron in South Africa has been reported for the 2-dose Pfizer and JnJ vaccines, largely in the absence of Omicron neutralizing Abs[12,13]. Additionally, T-cell responses appear more durable than serum NAb titers for all the vaccines which impacts boosting considerations[14].

While important for protection, Abs alone may not be sufficient to protect against disease. In support of this, a pre-clinical study demonstrated lack of protection in some vaccinated nonhuman primates with moderate Omicron NAb titers but undetectable Omicron specific CD8 T cells[15]. Furthermore, depletion of CD8 T cells in convalescent macaques partially abrogated protection against SARS-CoV-2 rechallenge, suggesting a role for cellular immunity in the settings of waning antibody titers[16]. Yet, neutralizing Ab activity continues to serve as the primary immune response measure evaluated by the FDA for modified COVID-19 vaccines and in "immune-bridging" studies of in pediatric cohorts.

As the pandemic continues to evolve, our response must as well. Emphasis on T-cell immunity will be particularly important moving forward for durable protection against severe disease with variants that largely escape NAb response. We need a concerted effort to collect data on the broad immune response beyond Abs, especially for our most vulnerable, to best inform public health strategies and federal policy decisions. We need clinical trial protocols that include investigations of the full range of adaptive immune responses in order to ensure that countermeasures keep pace with an evolving virus and lay the foundation for responses to future epidemics and pandemics. We need research funded and conducted by government agencies involving the human adaptive immune response to help deliver actionable correlates of protection to decision makers and reduce misinformation surrounding COVID-19. We pledge to work with you to provide robust science and evidence to support these efforts.

We are sincerely grateful for your tremendous efforts and commitment to leading America – and the world – through this crisis.

Sincerely,

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References:

1. IMPACC Manuscript Writing Team on behalf of the IMPACC Network Steering Committee. Immunophenotyping assessment in a COVID-19 cohort (IMPACC): A prospective longitudinal study. *Science Immunology*. 2021. doi:10.1126/sciimmunol.abf3733.
2. Harpaz R, Dahl RM, Dooling KL. Prevalence of immunosuppression among US adults, 2013. *JAMA*. 2016;316(23):2547–2548. doi:10.1001/jama.2016.16477.
3. Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature.* 2022;603(7901):488-492. doi:10.1038/s41586-022-04460-3.
4. GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS-CoV-2 Omicron-reactive T and B cell responses in COVID-19 vaccine recipients. *Sci Immunol*. 2022;7(69):eabo2202. doi:10.1126/sciimmunol.abo2202.
5. Liu J, Chandrashekar A, Sellers D, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 Omicron. *Nature*. 2022;603(7901):493-496. doi:10.1038/s41586-022-04465-y.

6. Tarke A, Coelho CH, Zhang Z, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. *Cell*. 2022;185(5):847-859.e11. doi:10.1016/j.cell.2022.01.015.
7. Gao Y, Cai C, Grifoni A, et al. Ancestral SARS-CoV-2-specific T cells cross-recognize the Omicron variant. *Nat Med*. 2022;28(3):472-476. doi:10.1038/s41591-022-01700-x.
8. Tada T, Zhou H, Samanovic M, et al. Comparison of neutralizing antibody titers elicited by mRNA and adenoviral vector vaccine against SARS-CoV-2 variants. *bioRxiv*. 2021. doi:11.1101/2021.07.19.452771.
9. Jongeneelen M, Kaszas K, Veldman D, et al. Ad26.COV2.S elicited neutralizing activity against Delta and other SARS-CoV-2 variants of concern. *bioRxiv*. 2021. doi:10.1101/2021.07.01.450707.
10. Corchado-Garcia J, Zemmour D, Hughes T, et al. Analysis of the effectiveness of the Ad26.COV2.S adenoviral vector vaccine for preventing COVID-19. Jama Netw Open. 2021;4(11):e2132540. doi:10.1001/jamanetworkopen.2021.32540.
11. Bekker LG, Garret N, Goga A, et al. Effectiveness of the ADD26.COV2.S vaccine in health-care workers in South Africa (the Sisonke study): results from a single-arm, open-label, phase 3B, implementation study. Lancet. 2022;399(10330):1141-1153. doi:10.1016/S0140-6736(22)00007-1.
12. Collie S, Champion J, Moultrie H, et al. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *N Engl J Med.* 2022;386(5):494-496. doi:10.1056/NEJMc2119270.
13. Gray GE, Collie S, Garrett N, et al. Vaccine effectiveness against hospital admission in South Africa health care workers who received a homologous booster of Ad26.COV2 during an Omicron COVID19 wave: Preliminary results of the Sisonke 2 study. *medRxiv.* 2021. doi:10.1101/2021.12.28.21268436.
14. Collier AY, Yu J, McMahan K, et al. Differential kinetics of immune responses elicited by COVID-19 vaccines. *N Engl J Med.* 2021;385(21):2010-2012. doi:10.1056/NEJMc2115596.
15. Chandrashekar A, Yu J, McMahan K, et al. Vaccine protection against the SARS-CoV-2 Omicron variant in macaques. *Cell.* 2022;S0092-8674(22)00334-8. doi:10.1016/j.cell.2022.03.024.
16. McMahan K, Yu J, Mercado NB, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature.* 2021;590(7847):630-634. doi:10.1038/s41586-020-03041-6.