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LETTER TO THE EDITOR

Response to letter to the editor: the clinical utility of diagnostic T cell assays for COVID-19

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To the editor

Dear Sir,

We thank colleagues from Adaptive Biotechnologies for their interest in our paper outlining the urgent need for diagnostic laboratories to develop and offer T cell assays for COVID-19 [1]. A robust early T cell response is critical for both a mild course of disease as well as viral clearance. Long-term immune protection against SARS-CoV-2 also appears to be a function of memory T cells. High titers of neutralizing antibodies are likely to be a surrogate marker of a robust protective T cell response to SARS-CoV-2 [2].

There are many patients who were infected early in the pandemic, who did not have access to accurate RT-qPCR tests for COVID-19. In some of these cases, antibodies have waned, leaving such patients in a diagnostic vacuum. A substantial number continue to suffer disabling post-COVID symptoms, termed Long-COVID. Patients with Long-COVID experience a range of sequelae including severe fatigue, chest pain and neurological manifestations including impaired clarity of thought (brain fog), autonomic instability and memory loss [3]. Many patients with Long-COVID are unable to work. A diagnosis of prior COVID in these patients has implications for health insurance coverage in some countries. In New Zealand, if COVID-19 was contracted at work, such as healthcare or border workers, there are additional benefits from the Accident Compensation Corporation. This includes reimbursement for lost wages and assistance with rehabilitation costs.

A T cell assay may also be very helpful in identifying antecedent COVID-19 in patients presenting with a variety of clinical scenarios such as pulmonary fibrosis or myocarditis but with negative SARS-CoV-2 tests [1]. In low prevalence countries such as NZ, a positive SARS-CoV-2 T cell test will have a high positive predictive value. In high prevalence areas, clinical judgment will be needed to determine causality.

A T cell assay might be useful for identifying asymptomatic patients who may have recovered from COVID-19, whose antibodies have waned. Children in particular, appear to have a muted antibody response and may be the source of an infected cluster [4]. At this time it is unknown if these asymptomatic patients will experience long-term sequelae from the infection. A T cell assay may be helpful in retrospectively identifying infected clusters.

Many immunocompromised patients have sub-optimal responses to COVID-19 vaccines. This was recently seen in Israel, where most fully vaccinated patients experiencing breakthrough infections were immunocompromised [5]. These included patients with liver and kidney transplants, hematological malignancy and renal failure. Following vaccination, these immunocompromised patients mounted significantly lower titers of neutralizing antibodies to the SARS-CoV-2 receptor binding domain, likely to reflect impaired cellular immunity. The Israeli government is now advising immunocompromised patients to have a third dose of the Pfizer vaccine. The UK government may implement a three dose primary COVID-19 vaccination strategy for immunocompromised patients. As recently suggested, a T cell assay would allow a nuanced individualized approach to immunocompromised patients, where extra doses or combinations of vaccines could be administered to ensure an optimal cellular response to SARS-CoV-2 [2].

With greater numbers of infected plasma donors and others who have been vaccinated, subcutaneous and intravenous immunoglobulin (SCIG/IVIG) preparations will contain increasing titers of SARS-CoV-2 antibodies. The majority of patients with Common Variable Immunodeficiency Disorders (CVID) have sub-optimal responses to vaccines [6]. However two recent studies have shown there is a hierarchy of vaccine responses in such patients: tetanus toxoid and H. influenzae type B (HIB) vaccines

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elicit much greater antibody responses than diphtheria toxoid or Pneumovax® [7,8]. It is hoped COVID-19 vaccines, like tetanus toxoid and HIB, will elicit a robust immune response in most patients with CVID. Since most CVID patients are on SCIG/IVIG, a T cell assay is required to demonstrate antecedent infection or responses to COVID-19 vaccines.

Such a T cell assay could be of great benefit also for immunocompromised patients who are at risk of Chronic COVID, a dangerous stalemate between SARS-CoV-2 and a suboptimal cellular response [9]. Prolonged viral shedding in Chronic COVID-19 can lead to intra-host viral evolution resulting in vaccine and monoclonal antibody resistant strains [10]. Chronic COVID-19 could result in variants of high consequence and is a public health emergency, within a global crisis: It must be prevented at any cost. Demonstrating a robust T cell response following individualized SARS-CoV-2 vaccination will be of considerable reassurance to immunocompromised patients and their physicians [2]. In the future, it is possible therapeutic cloned epitope-specific T cells may rescue such patients from this life and death struggle.

The authors from Adaptive Biotechnologies describe the benefits and limitations of their T cell assay. They assess the T cell receptor (TCR) repertoire of patients who have either experienced COVID-19 or who have been vaccinated. Previous infection can be distinguished from vaccination by determining the presence of TCRs against either the nucleocapsid or envelope proteins. It requires access to Next Generation Sequencing. Their assay is likely to be beyond the budget of much of the world, where even basic testing remains a challenge. The TCR repertoire may not indicate the magnitude of the cellular response to SARS-CoV-2 or protection conferred by COVID-19 vaccines. It is also unlikely to provide information on cross-protection against other variants of concern. It is also not possible to identify the type of cell responding to SARS-CoV-2 or COVID-19 vaccine.

Assessing protection of immunodeficient patients who have been vaccinated is likely to require a quantitative functional assay based on T cell activation, proliferation or cytokine production. These assays including flow cytometry, ELISPOT, Interferon y production and ^{3}H-thymidine uptake were described in detail in our publication [1]. There are relatively few diagnostic laboratories with the expertise to rapidly implement functional T cell assays for COVID-19 to ISO 9001 and 17025 standards. It is likely more commercial vendors will develop such assays but rapid viral evolution could hinder the future utility of such tests.

The current ^{3}H-thymidine uptake assay which was developed at LabPlus at Auckland Hospital is based on experience in assessing T cell responses to vaccines in immunodeficient individuals [11,12]. T cell responses to the spike (S) glycoprotein will be assessed by T cell proliferation. Such an assay has the advantage in that the stimulating S glycoprotein can be changed, depending on the SARS-CoV-2 variant circulating in the local community. This test may offer valuable prognostic information on vaccine-induced cross-protection against variants of concern in immunocompromised patients. The large dynamic range of the assay will distinguish responses to common cold coronaviruses (HCoV) from SARS-CoV-2 infection and COVID-19 vaccines. This will allow the creation of diagnostic reference intervals for both adults and children. Depleting CD4+ or CD8+ cells may identify the type of memory T cell responding to SARS-CoV-2 or COVID-19 vaccine.

Immunocompromised patients with poor cellular responses following SARS-CoV-2 vaccination, identified from a T cell assay, may be candidates for novel antiviral therapies such as the NZACE2-Pātari project [13]. NZACE2-Pātari comprises modified ACE2 molecules (N90D, R273A) which will be administered during the nasal phase of the infection to intercept each wave of daughter virus, to mitigate the pulmonary and systemic phases of COVID-19 [14]. It may be of particular benefit to unvaccinated individuals or those with impaired cellular immunity.

Declaration of Interests

The SARS-CoV-2 T cell assay is not under consideration by LabPLUS, Auckland Hospital. The NZACE2-Pātari project has not received funding for human studies at this time and is undergoing in vitro testing against variants of concern. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed and would be pleased to share their protocols gratis.

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