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Terrific cells for SARS-CoV-2

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DECLARATION OF INTERESTS
S.G. have patent applications in the fields of cell and/or gene therapy for cancer, and is a consultant of TESSA Therapeutics, a DSMB member of Immatics, and has received honoraria from Tidal, Catamaran Bio, Sanofi, and Novartis within the last 2 years. None of these relationships conflict with the published work.

MAIN TEXT
Vasileiou and colleagues describe in their elegant work in this issue of Haematologica the development of an allogeneic, off-the-shelf, SARS-CoV-2 specific virus-specific T cell (VST) bank (1). While vaccines, monoclonal antibodies, and antivirals had a significant impact in reducing the morbidity and mortality associated with SARS-CoV-2 infection, there is a continued need to develop novel biotherapeutics. In this regard, numerous cell therapies are currently being developed for the prevention and treatment of SARS-CoV-2 infection, including VSTs, and unmodified or genetically modified NK cells (2). In addition, clinical studies are progress that explore the utility of cell products to modulate SARS-CoV-2 induced immune activation, including regulatory T cells and mesenchymal stem cells (2).

In their study, Vasileiou and colleagues initially examined T-cell responses to 4 structural proteins [spike (S), membrane (M), envelope (E), nucleocapsid (N)] and 14 non-structural/accessory proteins (NSPs/NPs) of SARS-CoV-2 in the peripheral blood of
convalescent patients. For detection of SARS-CoV-2 specific T-cell responses, they used pepmixes, which consists of 15 amino acid long peptides with an 11 amino acid overlap, spanning the entire amino acid sequence of the respective SARS-CoV-2 proteins. T-cell responses to S, M, and N dominated, a finding that was consistent with other studies (3, 4). T-cell responses to NSPs/NPs were in general low or undetectable; however, variable responses were observed against NSPs/NPs 4 and 7A. Based on these findings, the authors selected S, M, N, 4 and 7A for the generation of an allogeneic, off-the-shelf, SARS-CoV-2 specific VST bank.

SARS-CoV-2 specific VSTs were generated with a well-established method using pepmixes in the presence of interleukin (IL) 4 and IL7 (5). Generated VSTs were enriched in CD4+ T cells, had a predominant central memory phenotype, and were polyclonal as judged by TCR vß repertoire analysis. Predominance of CD4+ T cells in VST products has been observed for other viruses (5), and is most likely a reflection of the used cytokine cocktail (6). Functional analysis revealed that CD4+ T cells predominantly contributed to SARS-CoV-2 reactivity, and that these T cells were polyfunctional, recognizing multiple viral antigens, which should reduce the risk of immune escape. Importantly, the generated SARS-CoV-2 specific VSTs recognized pepmixes encoding S proteins of SARS-CoV-2 variant strains, including alpha, beta, gamma, delta, epsilon and kappa. This is consistent with other studies, which had reported that individuals, who were vaccinated with a SARS-CoV-2 vaccine developed T cell responses to variant strains (7).

Vasileiou and colleagues infused four COVID-19 patients with off-the-shelf VSTs, who received standard of care but were at high risk for progression to severe disease. VST infusions were well tolerated and only one patient developed cytokine release syndrome (CRS). In all infused patients, VSTs could be detected as determined by TCR deep sequencing analysis. COVID-19 infection resolved in three out of four patients. While these results are encouraging, the clinical study was closed to accrual ‘due to trial's eligibility criteria and the low census of hospitalized COVID-19 patients meeting eligibility criteria’ as stated on the ClinicalTrials.gov webpage for this study.

The study is noteworthy for several reason. First, it highlights that existing technologies to generate VSTs can be readily adapted to new viral pathogens such as SARS-CoV-2. Second, the generated SARS-CoV-2 specific VSTs were polyclonal and able to recognize numerous
SARS-CoV-2 variants, which is a significant advantage over other biologics, including monoclonal antibodies. Finally, it is the first clinical study in which an allogeneic off-the-shelf VST product was evaluated without prior evaluation in the donor derived hematopoietic cell transplant (HCT) setting. Where do cell therapies fit into our current treatment armamentarium for SARS-CoV-2 and its variants? The acute setting might be less than ideal as highlighted by the closure of this study. Given as prophylaxis to high-risk individuals might be more attractive, especially in the setting of iatrogenic immunosuppression, including post HCT or solid organ transplant, since these cells could be genetically modified to be resistant to immunosuppressive agents like calcineurin inhibitors (8). In addition, expressing other therapeutic molecules like tumor specific chimeric antigen receptors (CARs) might be an attractive approach to prevent relapse in the post HCT setting. In particular since potent vaccines are available to boost adoptively transferred CAR-expressing SARS-CoV-2 specific VSTs in contrast to CAR-VSTs that recognize other viruses (9). Finally, SARS-CoV-2 specific VSTs might be useful in treating symptoms associated with long COVID, similar to Epstein Barr Virus (EBV) specific VSTs for chronic EBV infections (10).

In conclusion, this study highlights the feasibility of generating an allogeneic, off-the-shelf, SARS-CoV-2 specific VST bank with broad specificity against SARS-CoV-2 strain variants. The initial clinical safety and efficacy data of off-the-shelf VSTs were encouraging, paving the way for future studies.
REFERENCES


