Terrific cells for SARS-CoV-2

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In this issue of *Haematologica*, Vasileiou and colleagues describe their elegant work on the development of an allogeneic, off-the-shelf, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific T-cell bank.[1] While vaccines, monoclonal antibodies, and antivirals have had a significant impact on reducing the morbidity and mortality of coronavirus disease 2019 (COVID-19), caused by 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 virus-specific T cells (VST), and unmodified or genetically modified natural killer cells.[2] In addition, clinical studies are currently exploring the utility of cell products, including regulatory T cells and mesenchymal stem cells, to modulate SARS-CoV-2-induced immune activation.[2]

In their study, Vasileiou and colleagues initially examined T-cell responses to four structural proteins (spike [S], membrane [M], envelope [E], nucleocapsid [N]) and 14 non-structural/accessory proteins (NSP/AP) of SARS-CoV-2 in the peripheral blood of convalescent patients. In order to detect SARS-CoV-2-specific T-cell responses, they used pepmixes, which consisted 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 NSP/NP were generally low or undetectable; however, variable responses were observed against NSP/AP 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 T-cell bank.

SARS-CoV-2-specific T cells were generated with a well-established method using pepmixes in the presence of interleukin-4 and interleukin-7.[5] The VST generated were enriched in $CD4^+$ T cells, had a predominant central memory phenotype, and were polyclonal as judged by T-cell receptor vβ 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 cytokine cocktail used.[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 T cells 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 found 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 VST; the patients received standard care but were at high risk of progressing to having severe disease. VST infusions were well tolerated and only one patient developed cytokine release syndrome. VST could be detected in all infused patients, as determined by T-cell receptor deep sequencing analysis. COVID-19 infection resolved in three out of the 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 VST can be readily adapted to new viral pathogens such as SARS-CoV-2. Second, the SARS-CoV-2-specific T cells generated 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 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 a more attractive option, especially in the setting of iatrogenic immunosuppression, including after hematopoietic cell transplantation (HCT) or solid organ transplantation, since these cells can be genetically modified to be resistant to immunosuppressive agents such as calcineurin inhibitors.[8] In addition, expressing other therapeutic molecules, including tumor-specific chimeric antigen receptors (CAR) 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 T cells in contrast to CAR-VST that recognize other viruses.[9] Finally, SARS-CoV-2-specific T cells might be useful for treating symptoms associated with long COVID-19, in a way similar to the use of Epstein-Barr virus-specific T cells for chronic Epstein-Barr virus infections.[10]

In conclusion, the study by Vasileious *et al.* highlights the feasibility of generating an allogeneic, off-the-shelf, SARS-CoV-2-specific T-cell bank with broad specificity against SARS-CoV-2 variants. The initial clinical safety and efficacy data of off-the-shelf VST were encouraging, paving the way for future studies.

Disclosures

SG has patent applications in the fields of cell and/or gene therapy for cancer, is a consultant for TESSA Therapeutics, is a member of the Data and Safety Monitoring Board of Immatics, and has received honoraria from Tidal, Catamaran Bio, Sanofi, and Novartis within the last 2 years. None of these relationships conflicts with the published work.

References

1. Vasileiou S, Hill L, Kuvalekar M, et al. Allogeneic, off-the-shelf, SARS-CoV-2-specific T cells (ALVR109) for the treatment of COVID-19 in high-risk patients Haematologica. 2023;108(7):1840-1850.
2. Conway SR, Keller MD, Bollard CM. Cellular therapies for the treatment and prevention of SARS-CoV-2 infection. Blood. 2022;140(3):208-221.
3. Keller MD, Harris KM, Jensen-Wachspress MA, et al. SARS-CoV-2-specific T cells are rapidly expanded for therapeutic use and target conserved regions of the membrane protein. Blood. 2020;136(25):2905-2917.
4. Bertoletti A, Le Bert N, Tan AT. SARS-CoV-2-specific T cells in the changing landscape of the COVID-19 pandemic. Immunity. 2022;55(10):1764-1778.
5. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2017;35(31):3547-3557.
6. Durkee-Shock J, Lazarski CA, Jensen-Wachspress MA, et al. Transcriptomic analysis reveals optimal cytokine combinations for SARS-CoV-2-specific T cell therapy products. Mol Ther Methods Clin Dev. 2022;25:439-447.
7. 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.
8. Peter L, Wendering DJ, Schlickeiser S, et al. Tacrolimus-resistant SARS-CoV-2-specific T cell products to prevent and treat severe COVID-19 in immunosuppressed patients. Mol Ther Methods Clin Dev. 2022;25:52-73.
9. Lapteva N, Gilbert M, Diaconu I, et al. T-cell receptor stimulation enhances the expansion and function of CD19 chimeric antigen receptor-expressing T cells. Clin Cancer Res. 2019;25(24):7340-7350.
10. Savoldo B, Huls MH, Liu Z, et al. Autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for the treatment of persistent active EBV infection. Blood. 2002;100(12):4059-4066.