REFERENCES

1. Fidanza A, Stumpf PS, Ramachandran P, et al. Single-cell analyses and machine learning define hematopoietic progenitor and HSC-like cells derived from human PSCs. *Blood*. 2020;136(25):2893-2904.
2. Dzierzak E, Bigas A. Blood development: hematopoietic stem cell dependence and independence. *Cell Stem Cell*. 2018;22(5):639-651.
3. Jacobsen SEW, Nerlov C. Haematopoiesis in the era of advanced single-cell technologies. *Nat Cell Biol*. 2019;21(1):2-8.
4. Oatley M, Bölükbası ÖV, Svensson V, et al. Single-cell transcriptomics identifies CD44 as a marker and regulator of endothelial to haematopoietic transition. *Nat Commun*. 2020;11(1):586.
5. Garcia-Alegria E, Menegatti S, Fadlullah MZH, Menendez P, Lacaud G, Kouskoff V. Early human hemogenic endothelium generates primitive and definitive hematopoiesis in vitro. *Stem Cell Reports*. 2018;11(5):1061-1074.
6. Menendez P, Wang L, Chadwick K, Li L, Bhatia M. Retroviral transduction of hematopoietic cells differentiated from human embryonic stem cell-derived CD45$^{(neg)}$PFV hemogenic precursors. *Mol Ther*. 2004;10(6):1109-1120.
7. Stumpf PS, Du D, Imanishi H, et al. Mapping biology from mouse to man using transfer learning. *bioRxiv*. 2019; doi:10.1101/2019.12.26.888842.
8. Popescu DM, Botting RA, Stephenson E, et al. Decoding human fetal liver haematopoiesis. *Nature*. 2019;574(7778):365-371.
9. Sugimura R, Jha DK, Han A, et al. Haematopoietic stem and progenitor cells from human pluripotent stem cells. *Nature*. 2017;545(7655):432-438.
10. Petazzi P, Torres-Ruiz R, Fidanza A, et al. Robustness of catalytically dead Cas9 activators in human pluripotent and mesenchymal stem cells. *Mol Ther Nucleic Acids*. 2020;20:196-204.

DOI 10.1182/blood.2020007864

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Keller et al, page 2905

Expanding the toolbox to combat a pandemic

Susan E. Prockop | Memorial Sloan Kettering Cancer Center

Understanding immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical for optimizing treatment of COVID-19. In this issue of *Blood*, Keller and colleagues[1] generated SARS-CoV-2–specific cytotoxic T lymphocytes (CTLs) from the blood of individuals recovered from infection. The rapid application of this good manufacturing practice (GMP)-compliant system raises the possibility that banked third-party SARS-CoV-2 CTLs could be used for treatment.

The first demonstration that transfer of viral specific CTLs could provide effective prophylaxis and treatment of infections in immunodeficient recipients was made >25 years ago.[2] Since that time, the field has advanced, and an estimated 500 individuals have been treated on phase 1, 2, and 3 trials, which demonstrated efficacy in preventing and treating Epstein-Barr virus, cytomegalovirus, adenovirus, BK virus, and human herpesvirus 6.[3] SARS-CoV-2 is a novel coronavirus, and the T-cell immune responses to the virus, both optimal and maladaptive, are not fully understood (reviewed by Chen and John Wherry[4]). Although the generation of SARS-CoV-2 CTLs is an incremental advance in adoptive T-cell therapies for viral infections, the power of the methodology is demonstrated by the rapid pivot to adapt these GMP-compliant processes to target a novel virus causing a global pandemic.

An important feature of treatment with adoptively transferred viral CTLs generated by in vitro expansion from seropositive immune competent donors is tolerability with a limited incidence of off-target autoimmunity, such as graft-versus-host disease. Recent efforts have seen progress in increasing the number of viruses targeted and improving accessibility to these therapies by more rapid production methods and/or the use of banks of "off-the-shelf" third-party products.[1,5] Progress in tracking the in vivo expansion and durability of the transferred T cells has not kept pace with the clinical expansion of these therapies, but novel approaches to immune monitoring and the potential for deep sequencing of infused populations are changing that. Meanwhile, commercialization of banked viral-specific T-cell therapies is on the horizon.

Most of the clinical experience thus far in adoptive therapy with CTLs has targeted reactivation of viral infections in patients with immunodeficiency. The close association between immunodeficiency and viral disease establishes the rationale for adoptive cellular therapy for treatment of infections. Our understanding of protective and inflammatory responses and COVID-19 disease course (reviewed in Kuri-Cervantes et al[6]) is informing our approaches to improving therapies. Ongoing efforts to prevent and treat COVID-19 with SARS-CoV-2–specific immunity include convalescent plasma, highly neutralizing antibody, and vaccination.

In this paper, Keller and colleagues describe the isolation and expansion of SARS-CoV-2 CTLs from 46 convalescent donors, most of whom had mild disease. They effectively generated SARS-CoV-2 CTLs from 58% of donors, including from individuals with (26/33) as well as without (5/12) detectable antibody responses. They also were able to generate SARS-CoV-2 CTLs from 2 of 15 unexposed donors. The authors examined the phenotype of SARS-CoV-2–directed T-cell populations in patients who have recovered from (in most instances) clinically mild infection. As in other reports using different techniques,[7] the expanded SARS-CoV-2 specific T-cell populations were predominantly CD4$^+$ T cells with a T helper phenotype that recognizes viral epitopes in conserved regions of structural proteins. In addition, the authors demonstrate that these expanded CD4$^+$ T cells have significant diversity and include small populations of activated effector memory and CXCR5$^+$ follicular helper T cells potentially critical to understanding links between T-cell and B-cell SARS-CoV-2–specific immunity.

Keller et al also identify viral-specific responses to a highly conserved "hotspot" in the C-terminus of the Membrane protein recognized by multiple donors through a shared class II DR 01:01 HLA allele. The hierarchy of immunodominance identified by Keller et al, defined as the percentage of individuals with a T-cell response to each of 3 structural

proteins: Membrane (59%), Spike (26%), and Nucleocapsid (22%), differs from that identified by Grifoni et al,[7] who found Spike-specific T cells in all of the convalescent donors they examined. These differences underscore the potential for variables, such as the severity of infection and latency from infection to evaluation to impact the immune response. Furthermore, by identifying immunodominant areas of the M protein, this study suggests that vaccines combining more than Spike protein antigens may mediate durable protective immunity that more closely mimics natural protection.

Characterization of viral CTLs for not only the viral epitope recognized but also the HLA allele that presents that epitope is critical to the application of adoptive therapy with banked, third-party T cells.[5] For example, Keller et al demonstrate that SARS-CoV-2 CTLs recognizing membrane peptide 37 (AA 145 to 160) are restricted in recognition of this peptide through HLA DRB1*1101. These T-cell lines can then be selected for use in recipients sharing this HLA allele. A bank of viral-specific T-cell lines restricted by a set of commonly inherited HLA alleles could support treatment of most of the world's population.

The isolation and expansion of T cells from individuals recovered from mild to moderate COVID-19 infections are an appealing way to mimic an adaptive rather than maladaptive immune response. Complicated questions remain, including whether adoptive transfer of CTLs will need to occur early after infection before a maladaptive immune response is established and which patients will need adoptive T-cell therapy. Although the presumption is that immunocompromised patients such as recipients of hematopoietic transplant are at high risk of COVID-19–related mortality, recent reports suggest that transplant recipients can have favorable outcomes.[8] In addition, although limited by small numbers, other reports suggest that in patients with specific immune deficiency disorders, the nature of the underlying defect may predict severity of infection, whereas in other disorders, the specific defect is not predictive.[9,10] Whether adoptive transfer of SARS-CoV-2–specific populations of well-characterized T cells will prevent or treat COVID-19 will need to be evaluated formally in clinical trials. However, answering these questions will be facilitated by the remarkably rapid addition of CTLs to the potential armamentarium against a global pandemic.

Conflict-of-interest disclosure: The author receives support for the conduct of sponsored trials from Atara Biotherapeutics, Mesoblast, and Jasper, is an inventor of IP licensed to Atara Biotherapeutics by MSKCC, has assigned all rights to MSKCC, and has no financial interest in Atara Biotherapeutics. ■

REFERENCES

1. 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.
2. Walter EA, Greenberg PD, Gilbert MJ, et al. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. *N Engl J Med*. 1995;333(16):1038-1044.
3. Sutrave G, Gottlieb DJ. Adoptive cell therapies for posttransplant infections. *Curr Opin Oncol*. 2019;31(6):574-590.
4. Chen Z, John Wherry E. T cell responses in patients with COVID-19. *Nat Rev Immunol*. 2020;20(9):529-536.
5. O'Reilly RJ, Prockop S, Hasan A, Doubrovina E. Therapeutic advantages provided by banked virus-specific T-cells of defined HLA-restriction. *Bone Marrow Transplant*. 2019; 54(S2 Suppl 2):759-764.
6. Kuri-Cervantes L, Pampena MB, Meng W, et al. Immunologic perturbations in severe COVID-19/SARS-CoV-2 infection. *bioRxiv*. 2020; doi:https://doi.org/10.1101/2020.05.18.101717.
7. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*. 2020;181(7): 1489-1501.e15.
8. Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation [published online ahead of print 8 September 2020]. *J Clin Invest*. doi:10.1172/JCI141777.
9. Meyts I, Bucciol G, Quinti I, et al; IUIS Committee of Inborn Errors of Immunity. Coronavirus Disease 2019 in patients with inborn errors of immunity: an international study [published online ahead of print 24 September 2020]. *J Allergy Clin Immunol*. 2020;S0091-6749(20)31320-8.
10. Quinti I, Lougaris V, Milito C, et al. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. *J Allergy Clin Immunol*. 2020;146(1):211-213.e4.

DOI 10.1182/blood.2020009408

LYMPHOID NEOPLASIA

Comment on Los-de Vries et al, page 2927

Chromosomes in breast lymphoma

Laurence de Leval | Lausanne University Hospital; Lausanne University

In this issue of *Blood*,[1] Los-de Vries and colleagues investigate genome-wide chromosomal copy gains and losses in breast impant–associated anaplastic large cell lymphomas (BIA-ALCLs) and identify that frequent losses at chromosome 20q13.13 are a characteristic genomic feature of this disease.

BIA-ALCL is a very rare T-cell lymphoma categorized in the current World Health Organization classification of lymphoid malignancies as a provisional entity. It is defined as a subtype of anaplastic lymphoma kinase (ALK)$^-$ anaplastic large cell lymphoma (ALCL), which arises in patients with breast implants inserted for either cosmetic or reconstructive purposes.[2] The disease typically presents as a late-onset pericapsular effusion (seroma-associated or in situ lymphoma) and is usually cured by complete surgical excision. Less commonly, patients are diagnosed with poor prognosis, advanced stage disease with an infiltrative tumor mass, or with regional lymph node involvement.[3] Since the first case was described in 1997, epidemiological studies have confirmed that there is a causal relationship to the presence of textured breast implants. Our current understanding of BIA-ALCL pathogenesis includes a chronic inflammatory/immune reaction elicited by the implant or bacteria adherent to it, with secondary genetic lesions mediating transformation, dependence on cytokine activation, and JAK-STAT pathway activation.[3,4]