Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Comment on Keller et al, page 2905

Expanding the toolbox to combat a pandemic

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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.

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LYMPHOID NEOPLASIA

Comment on Los-de Vries et al, page 2927

Chromosomes in breast lymphoma

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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]