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Adoptive T Cell Immunotherapy for Patients with Primary Immunodeficiency Disorders

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Abstract

Primary immunodeficiency disorders (PID) are a group of inborn errors of immunity with a broad range of clinical severity but often associated with recurrent and serious infections. While hematopoietic stem cell transplantation (HSCT) can be curative for some forms of PID, chronic and/or refractory viral infections remain a cause of morbidity and mortality both before and after HSCT. Although antiviral pharmacologic agents exist for many viral pathogens, these are associated with significant costs and toxicities and may not be effective for increasingly drug-resistant pathogens. Thus, the emergence of adoptive immunotherapy with virus-specific T lymphocytes (VSTs) is an attractive option for addressing the underlying impaired T cell immunity in many PID patients. VSTs have been utilized for PID patients following HSCT in many prior phase I trials, and may potentially be beneficial before HSCT in patients with chronic viral infections. We review the various methods of generating VSTs, clinical experience using VSTs for PID patients, and current limitations as well as potential ways to broaden the clinical applicability of adoptive immunotherapy for PID patients.

Keywords

Primary immunodeficiency; Cytotoxic T lymphocytes; Adoptive immunotherapy; Antiviral therapy; Hematopoietic stem cell transplantation

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Conflict of Interest Drs. McLaughlin, Bollard, and Keller declare no conflicts of interest relevant to this manuscript.

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Introduction

Primary immunodeficiency disorders (PID) are a group of inborn errors of immunity. To date, over 320 causative genes have been identified, which result in a wide spectrum of disorders ranging from profound immunodeficiency manifesting in the newborn period to immunologic disorders that can manifest in adulthood [1, 2]. Though autoimmunity and severe allergic disease are sometimes presenting signs of PID, recurrent and often serious infections are the most common presentation. Severe forms of PID such as severe combined immunodeficiency (SCID) often manifest in the newborn period with failure to thrive and susceptibility to a wide variety of pathogens [3]. Other forms of PID cause more narrow susceptibility to infections, such as the selective susceptibility to intracellular microbes caused by defects in the IL-12/IFN-γ pathway [4].

The use of hematopoietic stem cell transplantation (HSCT) has proven to be lifesaving for moderate to severe forms of PID [5, 6]. Though it has been the standard of care for SCID for over 40 years, HSCT is now increasingly being utilized to prevent late complications in other forms of PID such as chronic granulomatous disease, DOCK8 deficiency, GATA2 haploinsufficiency, and IPEX and related syndromes, such as individuals with STAT3 gain-of-function mutations [7–10]. In many of these forms of PID, patients often have a significant infectious burden at the time of diagnosis.

Chronic and refractory viral infections are a cause of significant mortality both before and after HSCT in patients with PID [11, 12, 13•]. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and respiratory viruses have been described as the leading causes of virus-associated mortality in this population, and accounted for up to 40% of transplant-related mortality [3, 5]. Though newborn screening for SCID has been tremendously successful in permitting early preventative treatments and definitive therapy prior to occurrence of severe infections [14], the vast majority of PID are not caught by the TREC assay. Antiviral pharmacotherapy is available for many viruses, but is often limited by toxicity and resistance [15–19]. Given the need for a conditioning (chemotherapy) regimen prior to HSCT for many forms of PID, active viral infections can pose serious risks for patients undergoing transplantation for PID [13•].

Reconstitution of T cell immunity is critical for control of viral infections. However, the emergence of naïve T cells usually does not occur for 3–6 months after HSCT and may be further delayed in the setting of cord blood transplantation or with the occurrence of graft-versus-host disease (GVHD) [20, 21]. During this period, patients remain profoundly susceptible to viral infections. Infusion of unmanipulated donor lymphocytes has been a successful strategy to combat persistent viral infections after HSCT, but this approach risks severe GVHD [22–24]. Adoptive immunotherapy with virus-specific T lymphocytes (VSTs) allows reconstitution of antiviral immunity after HSCT and has been effective for treatment or prevention of viral infections with CMV, EBV, and adenovirus (AdV) with minimal risk of GVHD [25, 26]. Though most prior studies have utilized VSTs generated from the HSCT donor, more recently the use of banked, partially HLA-matched VST from third party donors has permitted "off the shelf" therapy for critically ill patients [27]. Thus, it is possible to circumvent the need for a unique donor and the time required for VST production.

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Over 400 patients have been treated with VSTs in previous phase I and II trials, with the majority of patients being treated following HSCT. As PID represents a sizeable proportion of the non-malignant referrals for HSCT in pediatrics, patients with PID have been represented in many prior VST trials. Here, we review the prior use of VST therapy for patients with PID, as well as upcoming trials and advances in adoptive immunotherapy, and how it may impact the future care of patients with PID.

VST Generation Methods

Adoptive T cell therapy for viral infections has been successfully used clinically for over 20 years [28, 29•]. While unmanipulated donor lymphocyte infusions (DLIs) are capable of restoring virus-specific immunity after HSCT, this approach increases the risk of GVHD [30]. Early studies demonstrated that selective transfer of antigen-specific T cells, isolated via ex vivo expansion or multimer selection, decreased the risk of GVHD [31–33].

Initial adoptive T cell therapy methods relied on prolonged ex vivo culture methods by which the desired virus-specific T cells would be activated and expand in the setting of stimulation with cytokines while alloreactive cells would die in culture. Early culture methods required not only being able to identify the immunogenic antigens but also having antigen presenting cells (APCs) that could not only present the target antigens but also provide costimulatory molecules to promote T cell activation and expansion. Dendritic cells (DCs), activated monocytes, phytohemagglutinin blast (PHA blasts), and lymphoblastoid cell lines (LCLs) may be used as APCs, but using APC to multiply stimulate VSTs does increase the time and complexity of the manufacturing process [31, 34••]. Viruses or viral lysates have been used as antigen sources, but the advent of synthetic peptide pools that span immunodominant proteins has improved culture protocols by eliminating the risk of live viral transduction, and allowing expansion of T cells with a variety of HLA restrictions [35]. Rapid ex vivo culture methods using a single stimulation with APC pulsed with synthetic peptide pools can shorten the duration of manufacturing to approximately 10 to 14 days while maintaining antigen specificity and achieving the cellular expansion needed for clinical use.

While the rapid ex vivo expansion of VSTs has appreciably reduced manufacturing time and costs, VSTs can be produced even more rapidly using selection techniques such as multimer selection or IFN-γ capture [36–38]. In multimer selection, magnetically labeled peptide multimers are used to select T cells that are reactive to immunogenic peptides. Similarly, IFN-γ capture selects T cells that produce IFN-γ in the presence of stimulation by viral antigens using an immunomagnetic separation device. While these techniques can provide a product within 24 to 48 h, they require the donor to be immune to the virus(es) of interest and a high number of circulating reactive T cells in the starting product. Therefore, apheresis is often needed to procure the number of T cells needed for clinical use, and antigen-specific T cell yields are typically limited. Multimer selection is an HLA-restricted process, but IFN-γ capture has the advantage of not being HLA-restricted and produces a product that contains $CD4^+$ and $CD8^+$ T cells that recognize targeted viral epitopes.

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Clinical Experience Using VSTs for PID Patients

Studies Utilizing Ex Vivo Expansion Methodologies

Numerous immunodeficiencies such as X-linked lymphoproliferative disorder and familial hemophagocytic lymphohistiocytosis (FHLH) are commonly associated with EBV-related complications ranging from fulminant mononucleosis to lymphoproliferative disorders and EBV-related lymphomas [39]. As these complications are secondary to ineffective EBV-specific T cell surveillance allowing for uncontrolled proliferation of EBV-infected B cells, adoptive T cell therapy with EBV-specific T cell therapy is a logical therapeutic option as it addresses the underlying immune deficit. Heslop et al. treated 101 patients at risk for EBV-related lymphoproliferative disease prophylactically and 13 patients therapeutically with EBV-specific T cells generated using LCLs as antigens presenting cells [40••, 41]. This cohort included 13 patients with PID. Remarkably, none of the patients in the prophylaxis cohort developed lymphoproliferative disease, and 11 of the 13 patients treated therapeutically had complete remissions. Seven of the PID patients in the prophylaxis cohort had EBV viremia at the time of infusion, four of whom had resolution of viremia, and the remaining three had decreases in EBV viral load without clearance.

To expand the clinical applicability of VST, Leen et al. demonstrated that CMV, EBV, and AdV-specific T cells can be manufactured in a monoculture using EBV-LCLs transduced with an adenoviral vector expressing CMV-pp65 protein (Ad5f35-CMVpp65) and can produce clinically relevant effects [34••]. Eleven patients, including one with SCID, received VST infusions, and all patients with active infection at the time of infusion had resolution of viral symptoms and reduction in viral titers. However, it was noted that while EBV and CMV-specific T cells expanded in all patients within 4 weeks of infusion, AdV-specific T cells only expanded in patients with recent or active AdV infections. As these trivirus-specific products were dominated by CMV-reactive T cells, the culture method was modified to use LCLs transduced with a Ad5f35 vector to produce bivirus (EBV and AdV) specific T cell products [42]. This resulted in a higher frequency of AdV-reactive T cells in the products compared to the trivirus products. Thirteen patients, including one patient with SCID, received bivirus-specific T cell products in a phase I protocol. While AdV-specific T cells again only expanded in vivo in patients with concomitant AdV infections, none of these patients developed de novo AdV infections, suggesting that infused products had in vivo activity even if below the detectable level by ELISpot assay.

Despite these clinical successes, the time and cost associated with these prolonged culture methods limited their clinical use. Thus, several groups have subsequently developed rapid culture methods that have demonstrated safety and efficacy in clinical trials. Bao et al. used a rapid culture method using peptide pools for CMV pp65 and IE1 to produce CMV-specific T cell products from 10/10 healthy HSCT donors, and seven patients met eligibility criteria for infusion, four of whom were transplanted for immunodeficiencies [43]. Two of the PID patients had complete resolution of CMV infection, and one patient had a transient response but developed recurrence of CMV viremia after steroids were initiated for flare of HLH. The fourth patient had undetectable CMV-specific T cell function noted after infusion and persistent viremia, but the authors hypothesized that efficacy was diminished by the poor

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viability (60%) of the infused product as the patient subsequently demonstrated an increase in CMV-pp65-specific cytotoxic activity 3 weeks after receiving an unmodified DLI.

Papadopolou et al. demonstrated that a rapid ex vivo culture method can be used to generate VSTs specific for CMV, EBV, AdV, HHV6, and BK virus, although only 14 of 48 products generated had specificity for all five viruses [44••]. Four of the 11 patients treated had received an HSCT for PID conditions. All four patients had complete responses to targeted viruses, with the exception of one patient with HLH who had a complete response to HHV6 and EBV but no response to BK virus, which was not surprising as the infused product lacked specificity for BK. Overall, this study demonstrated a 94% response rate (15 CR; 2 PR) for the 18 viral infections/reactivations observed. Three patients who received VSTs for prophylaxis did not develop any viral complications.

Several previously unpublished cases were also included in a recent retrospective review by Naik et al. [45••]. Five patients with PID received trivirus-specific VST derived from their HSCT donor at our institution, including two with SCID, one with Wiskott-Aldrich Syndrome, and one with HLH due to STXBP2 deficiency. Three of these patients had existing viral infections (CMV in two, and CMV and EBV in 1), and two patients were treated prophylactically. Four of the five patients cleared their targeted infections and subsequent reactivations, while a fifth patient with SCID had progressive viral disease.

Patients Treated with “Third Party” VSTs

Third party banks of VSTs can further increase the availability of cellular therapy for patients with viral infections as they are not only readily available “off-the-shelf” but also provide therapeutic options for patients for whom custom-made products would not be available if they had a seronegative donor (e.g., cord blood). Although the experience using third party VSTs in PID patients has been limited thus far (Table 1), a multicenter phase I study demonstrated a 74% response rate in 50 patients who had undergone HSCT for various underlying diagnoses [46••]. Doubrovina et al. also described a series of 49 patients who were treated for EBV-lymphoproliferative disease following HSCT with donor lymphocyte infusion and/or EBV-specific VST that were either HSCT-donor derived or third party. Three patients in this series had PID disorders: one with autoimmune lymphoproliferative syndrome, one with X-linked lymphoproliferative disease, and another had primary HLH. The authors described an overall response rate of 68% following EBV-specific VST infusion, including a complete response in the patient with HLH who received third party EBV-specific T cells [24].

Third party products may be of potential use pre-HSCT for PID patients, who are particularly susceptible to viral infections even before HSCT. Among the patients reviewed by Naik et al., two patients with PID (one with SCID and another with CTPS1 deficiency) were treated for persistent viral infections with VST derived from partially HLA-matched third party donors prior to HSCT. The latter patient, who had EBV-associated CNS lymphoma, had complete resolution of the lymphoma and clearance of EBV viremia after receiving EBV-specific VST prior to umbilical cord blood transplantation [47, 48].

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Patients Treated with VST Derived Via Selection Technology

Several groups have utilized selection technology to treat viral infections in patients with PID following HSCT. Feuchtinger et al. treated nine patients with AdV-specific T cells isolated with IFN-γ capture, including one patient with HLH. Five out of six evaluable patients including the patient with HLH had in vivo expansion of the infused VST and durable antiviral responses [49]. These successes occurred in spite of low cell doses (1.2–5 × 10 [3] cells/kg) obtained by selection methods. Qasim et al. treated five patients with adenoviremia post-HSCT (including one with combined immunodeficiency, one with X-linked SCID, and one with MHC class-II deficiency) with AdV-specific VST derived via their HSCT donor or a parental donor [50]. Two of the treated patients had resolution of AdV infection and survived, while three died (two due to viral progression and one due to GVHD).

A recent French multicenter pilot study (NCT01325636) treated 15 patients after HSCT with CMV and/or AdV infections with VSTs generated by IFN-γ capture [51]. Five patients in this cohort had undergone HSCT due to PID. Three of the five PID patients demonstrated in vivo expansion of VSTs at day +21 of which two patients had stabilization of their retinitis while the third patient remained alive but blind. Two additional PID patients died of pulmonary complications in the setting of ongoing viral infections. Of those treated, one patient developed grade III GVHD in the 3 weeks after VST infusion, and another patient developed chronic GVHD.

Feucht et al. treated thirty patients with AdV infections, including seven with immunodeficiency, with hexon-specific T cells isolated by IFN-γ capture [52]. Twenty-one patients responded to VST infusion, including complete viral clearance in 18 patients and 3 partial responses (>1 log decrease in viral load without clearance). Two of the responders still died from AdV infection, and all eight of the non-responders died from progressive AdV disease. In this cohort, two patients developed grade I GVHD after VST infusion.

Potential Risks of VSTs

Multiple phase I studies have shown VSTs to be safe and well-tolerated. Infusion reactions are uncommon and mild and likely related to the cryopreservation additive rather than the VST themselves. While unmanipulated DLIs are capable of restoring virus-specific immunity after HSCT [30], this approach increases the risk of GVHD [22]. In contrast, the use of ex vivo expansion or direct selection methodologies to generate VSTs decreases the GVHD risk by reducing the alloreactive cells in the final product [21, 53]. In the largest retrospective review of VSTs in PID patients, only 4 of 36 patients (11%) had evidence of GVHD. Three patients developed GVHD in the setting of weaning of immunosuppression and responded well to steroid therapy. As control groups were not built into any phase I protocols to date, it is unclear if the rate of GVHD in those receiving VST therapy is different from the background rate of GVHD in patients undergoing HSCT. The risk of GVHD has been similarly low even when VSTs are only partially HLA matched such as those derived from haploidentical or third party donors [27, 46••].

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Cytokine release syndrome (CRS), which can present with fever, hypotension, and multi-organ dysfunction due to immune-mediated inflammation, is another potential risk of antiviral cellular therapy. CRS has been well-described in the setting of chimeric-antigen receptor (CAR) T cell therapy and is associated with elevations in serum cytokines including IL-6, TNFα, and IFNγ [54]. Rooney et al. described inflammatory complications requiring mechanical ventilation in one patient with bulky EBV-related disease, who subsequently had a complete remission [41]. To date, CRS has not been described in patients with PID who have been treated with VST therapy, though it remains a theoretical risk, particularly in patients with disseminated viral disease.

Limitations of Current VST Protocols

Though CMV, EBV, and AdV are the most common viral pathogens associated with morbidity and mortality after HSCT for PID, many other viral infections are a threat to patients with PID, both before and after transplantation [11, 55]. Papadopoulou et al. expanded VST therapy to include targeting of HHV6 and BK virus with clinical success [44••]. While increasing the number of viruses targeted with a single product is appealing, it raises concern for antigenic competition in which the resulting products would be skewed toward immunodominant viral antigens. However, while CMV-pp65 and CMV-IE1 are considered strongly immunogenic, Papadopoulou et al. showed that CMV was the least consistently recognized virus in their VST products (26 of 48 VSTs) while AdV was the most consistently recognized virus (45 of 48 VSTs). Indeed, viral specificity of VSTs seemed more closely associated with pre-existing donor immunity, as all 26 VSTs derived from CMV-seropositive donors were specific for CMV whereas none of the VSTs derived from CMV-seronegative donors showed specificity for CMV antigens. Moreover, they demonstrated that there was no significant difference in the number of AdV-reactive T cells in a product regardless of the number of viruses the product was specific for. Hence, they proposed that virus-specificity in the multivirus T cell products is dependent on the frequency of pre-existing virus-specific T cells in the donor.

In the setting of partially HLA-matched third party VST therapy, a comparison of clinical outcomes using “overall best HLA match” strategies versus the approach utilized by Leen et al., where antiviral restrictions of selected VST products were confirmed prior to use, suggests that confirmation of antiviral activity mediated through one or more shared HLA alleles is essential for clinical efficacy [46••]. Accordingly, an improved knowledge of the antiviral restrictions of a multitude of viral antigens will be necessary in order to extend third party therapy to a wider number of pathogens.

Future Directions

Extending to Other Viruses

As VSTs have shown to be safe and efficacious in multiple phase I studies, there is growing interest in targeting other pathogens with cellular therapy. Human parainfluenza (HPIV) is a common respiratory pathogen that causes mild disease in immune competent hosts but causes significant morbidity and mortality in immune-compromised patients such as those with PID, with HPIV3 being the most common serotype in the post-HSCT setting [11,

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56]. Currently, no therapeutic options exist for HPIV infections other than supportive care. Preclinical studies demonstrated that HPIV3-specific T cells can be generated from healthy donors using a rapid ex vivo culture protocol using peptide stimulation [57]. Importantly, HPIV3 could be targeted alongside EBV, CMV, AdV, BK, and HHV6 using this same method without loss of HPIV3-specificity.

Patients undergoing HSCT receive routine antiviral prophylaxis against herpes simplex virus (HSV); however, patients remain at risk from reactivation or infection with drug-resistant strains. HSV-1-specific T cells have been generated from seropositive donors using a culture method with antigen-pulsed dendritic cells and demonstrated cytokine production and cytotoxicity against HSV-1-infected targets [58]. Both of these promising preclinical studies will hopefully be translated into the clinical trials in the near future.

Extending to Other Pathogens

While viruses are a significant cause of morbidity and mortality both pre- and post-HSCT in patients with PID, many patients with PID are also risk for invasive fungal and mycobacterial infections [4, 59, 60]. Perruccio et al. treated 10 patients after HSCT with *Aspergillus*-specific T cells, and 9 patients had resolution of invasive aspergillosis [61]. Admittedly, the importance of T cell immunity in combating invasive aspergillosis is still unclear, as previous studies have demonstrated robust T cell immunity against *Aspergillus* species in patients with chronic granulomatous disease [62]. Invasive mycobacterial infections are unfortunately often a presenting sign in patients with T cell deficiency who receive early immunization with the live *Bacillus Calmette-Guerin* (BCG) vaccine [63]. Smith et al. published a report of a patient with SCID and disseminated BCG, which persisted after unfractionated HSCT despite therapy with multiple antibiotics [64]. She was given multiple whole blood transfusions from a healthy, HLA-matched sibling who previously had been immunized with BCG. Gradual improvement in radiographic lesions was noted with no evidence of GVHD, and a strong proliferative response was detectable in response to purified protein derivative. This case demonstrated that adoptive immunotherapy for mycobacteria may be feasible, and given the problem of multidrug resistance in many species of mycobacterial, T cell therapy may be an extremely useful adjunctive therapy.

Optimizing Manufacturing

Despite improvements in manufacturing time and costs, cellular therapy with VSTs remains a limited therapeutic option as it is only available at specialized centers with Good Manufacturing Practice (GMP)-compliant facilities capable of generating clinical grade products and meeting regulatory guidelines. As the use of third party VST improves, the use of specialized centers as regional banks, as well as commercialization of T cell banks should dramatically improve the availability of “off the shelf” VST products. The use of commercially available selection kits may also widen the availability of T cell therapy.

Conclusions

While numerous phase I studies have demonstrated the efficacy and safety of VSTs, comparing outcomes from various studies is complicated not only by the various

manufacturing methods but also by the variation in cell doses and viruses targeted. Moreover, patients with PID are an extremely heterogeneous population and have variable HSCT regimens. Thus, there exists a considerable need for larger, multi-institutional phase II studies and meta-analyses to determine optimal manufacturing methods, dosing, and timing as well as long-term outcomes for patients treated with VSTs. However, adoptive T cell immunotherapy will likely become an integral component of transplantation, particularly as advances are made in the range of targeted pathogens and in the understanding of essential T cell subsets that can rapidly and safely target infections in immunocompromised patients.

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Table 1

Patient characteristics and outcomes of PID patients treated with VSTs

Reference	PID diagnosis	Infection	Specificity	VST stimulation	Source	Cell dose	Outcomes
Bao et al. [43]	Hyper IgM syndrome	CMV	CMV	Culture, peptide	HSCT donor, peripheral blood	5×10^5/kg	Persistent viremia
	SCID	CMV	CMV	Culture, peptide	HSCT donor, peripheral blood	5×10^5/kg	Resolution of viremia
	CID	CMV	CMV	Culture, peptide	HSCT donor, peripheral blood	2.5×10^5/kg	Resolution of viremia
Creidy et al. [51]	FHLH	Meningoecephlitis; retinitis	AdV	Selection by IFN-γ secretion	Haploidentical HSCT donor, leukaphresis	(1) 5×10^4/kg (2) 1.5×10^4/kg	Alive, stabilization of retinitis
	SCID	Meningoecephlitis; retinitis	AdV	Selection by IFN-γ secretion	Haploidentical HSCT donor, leukaphresis	(1) 5×10^4/kg (2) 5×10^4/kg	Resolution of viremia; stabilization of retinitis
	FHLH	Pneumonitis; encephalitis; retinitis; viremia	CMV	Selection by IFN-γ secretion	HSCT donor, leukaphresis	1.76×10^4/kg	Died at day +3 (alveolar hemorrhage)
	FHLH	CMV viremia	CMV	Selection by IFN-γ secretion	Haploidentical HSCT donor, leukaphresis	(1) 3×10^4/kg (2) 5.88×10^4/kg (3) 1.99×10^5/kg	Died at day +96; pulmonary arterial hypertension
	CID	Retinitis	CMV	Selection by IFN-γ secretion	HSCT donor, leukaphresis	5×10^4/kg	Alive but blind
Feuchtinger et al. [37]	HLH	AdV viremia, diarrhea	AdV	Selection by IFN-γ secretion	HSCT donor, peripheral blood	5×10^4/kg	Clearance of AdV from blood and stool
Leen et al. (2006) [34••]	SCID	Adeno	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMV pp65 vector	HSCT donor, peripheral blood	$1 \times 10^8/m^2$	Clearance of AdV
Leen et al. (2009) [42]	SCID	Prophylaxis	EBV, AdV	Culture, LCL with Ad5f35 vector	HSCT donor, peripheral blood	$1.35 \times 10^8/m^2$	Alive, no active infections
Papadopolou et al. [44••]	LAD	Adenoviremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	Haploidentical HSCT donor, peripheral blood	$2 \times 10^7/m^2$	CR
	GATA2	EBV, BK viremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	CR
	SCID variant	BK viremia; EBV viremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	CR
	HLH	HHV6, BK viremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	HSCT donor, peripheral blood	$1 \times 10^7/m^2$	HHV6: CR; BK: NR; EBV: CR
Vickers et al. [48]	CID	PTLD (EBV)	EBV	Culture, LCL	Third party	$1–2 \times 10^6$/kg/dose; 4 doses given weekly	CR
	CGD	PTLD (EBV)	EBV	Culture, LCL	Third party	$1–2 \times 10^6$/kg/dose; 4 doses given weekly	PD; died

Reference	PID diagnosis	Infection	Specificity	VST stimulation	Source	Cell dose	Outcomes
	CID	PTLD (EBV)	EBV	Culture, LCL	Third party	$1–2 \times 10^6$/kg/dose; 4 doses given weekly	PD; died
Wynn et al. [47]	CTPS1	Primary CNS Lymphoma	EBV	Culture, LCL	Third party	2×10^6/kg/dose; 7 doses given weekly; 2 additional doses given after re-emergence of EBV disease	CR
Heslop et al. [40••]	WAS	EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	CR
	NK defect/ SCAEBV	EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$1 \times 10^8/m^2$	CR
	SCAEBV	EBV	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	PR, died of progressive lymphoma
	SCAEBV	EBV-LPD	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	No further EBV reactivation
	XLP (SLAM mutation)	EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	CR
	XLP and lymphoma	Prophylaxis	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	No viremia
	CID, enterocolitis	EBV-LPD (EBV viremia resolved)	EBV	Culture, LCL	HSCT donor, peripheral blood	$2.5 \times 10^7/m^2$	No further EBV reactivation
	WAS	EBV-LPD (EBV viremia resolved)	EBV	Culture, LCL	HSCT donor, peripheral blood	$2.5 \times 10^7/m^2$	No further EBV reactivation
	XLP	Resolved EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	No further EBV reactivation
	XLP	EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	PR
	XLP	Resolved EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	CR
	XLP	EBV-LPD with viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	PR
	XLP-like	Resolved EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/m^2$	No further EBV reactivation
Doubrovina et al. [24]	HLH	EBV-LPD	EBV	Culture, LCL	HSCT donor, peripheral blood	1×10^6/kg × 3 doses	PD; died
	XLP	EBV-LPD	EBV	Culture, LCL	Third Party	1×10^6/kg × 3 doses	CR
	ALPS	EBV-LPD	EBV	Culture, LCL	HSCT donor, peripheral blood	1×10^6/kg	NE; died
Naik et al. [45••]	IL7RA-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor, umbilical cord	$1.5 \times 10^7/m^2$	No viremia

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Reference	PID diagnosis	Infection	Specificity	VST stimulation	Source	Cell dose	Outcomes
	IL2RG-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor, umbilical cord	$2.5 \times 10^7/m^2$	No viremia
	IL2RG-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor, umbilical cord	$1 \times 10^7/m^2$	No viremia
	IL2RG-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor	$1 \times 10^7/m^2$	No viremia
	SCID	Prophylaxis	AdV	Culture, DC and LCL with Ad5f35 vector	HSCT donor	$1 \times 10^7/m^2$	No viremia
	MHC II deficiency	CMV viremia, pneumonitis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor	$1 \times 10^7/m^2$	CR
	WAS	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor	$1 \times 10^7/m^2$	No viremia
	CID, enterocolitis	Prophylaxis	EBV	Culture, peptide	HSCT donor	$2.5 \times 10^7/m^2$	No viremia
	ADA-SCID	EBV-LPD	CMV, EBV, AdV	Culture	Third party	$5 \times 10^6/m^2$	NR, died from EBV lymphoma
	SCID	CMV viremia	CMV, EBV, AdV	Culture	HSCT donor	$5 \times 10^6/m^2$/dose; 2 doses	PR
	SCID	(1) CMV viremia (2) CMV viremia and pneumonitis	(1) CMV, EBV, AdV (donor) (2) CMV, EBV, AdV (third party)	Culture	HSCT donor	(1) $1 \times 10^7/m^2$ (2) $2 \times 10^7/m^2$	NR; died; refractory CMV and disseminated BCG
	MHC II Deficiency	Prophylaxis	CMV, EBV, AdV	Culture	HSCT donor	$5 \times 10^6/m^2$	CMV: CR
	HLH (STXBP2)	CMV, EBV viremia	CMV, EBV, AdV	Culture	HSCT donor	$1 \times 10^7/m^2$/dose × 2 doses	CMV: CR; EBV: CR
	WAS	Prophylaxis	CMV, EBV, AdV	Culture	HSCT donor	$2 \times 10^7/m^2$	
	IL-10R deficiency	AdV viremia, pneumonitis	CMV, EBV, AdV	Culture	Third party	$2 \times 10^7/m^2$	AdV: CR; CMV: CR
	CTPS1	EBV-LPD	EBV	Culture	Third party	2×10^6/kg/dose × 2 doses	CR
	HLH	EBV viremia	EBV	Culture	Third party	2×10^6/kg/dose × 3 doses	EBV: PR; died; PTLD
	CD4 lymphopenia	CMV viremia	CVM	Multimer selection	HSCT donor	2×10^6/kg	CMV: PR; died of fungal pneumonia

SCID severe combined immunodeficiency, *CID* combined immunodeficiency, *FHLH* familial hemophagocytosis lymphohistiocytosis, *LAD* leukocyte adhesion deficiency, *CGD* chronic granulomatous disease, WAS Wiskott-Aldrich Syndrome, *SCAEBV* severe chronic active Epstein-Barr virus infection, *XLP* X-linked lymphoproliferative syndrome, *ALPS* autoimmune lymphoproliferative syndrome, *CTPS1* cytidine-5-prime-triphosphate synthetase, *CR* complete response, *PR* partial response, *PD* progressive disease, *NR* no response, *NE* not evaluable