Adoptive T cell therapy for the treatment of viral infections

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Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for a variety of malignant and non-malignant hematological disorders. However, many features of transplantation, including the immunosuppressive drugs administered as pre-transplant conditioning as well as the agents administered post-transplant to prevent graft versus host disease (GvHD), serve to compromise the host immune system leaving patients vulnerable to an array of latent and lytic viruses including cytomegalovirus (CMV), adenovirus (AdV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6) and BK virus (1-4). Conventional therapy for these infections has relied largely upon the use of small molecule antiviral drugs such as ganciclovir (for CMV and HHV6), cidofovir (for AdV and BK) and foscarnet (for CMV) (5-7). However, prolonged use can lead to toxic side effects such as bone marrow suppression (8) and nephrotoxicity (9), as well as the emergence of drug-resistant mutants (10) (e.g., ganciclovir-resistant CMV). Furthermore, since none of these agents improve endogenous virus-specific T cell (VST) immunity, infections frequently recur upon treatment termination, highlighting the need for novel therapies. This has prompted a number of groups, including our own, to evaluate the therapeutic benefits associated with the adoptive transfer of *in vitro* expanded VSTs and since the mid-1990s we have undertaken a series of clinical trials using stem cell donor-derived T cell lines targeting one or more of these clinically problematic viruses (11,12). Our recent study (13) reports on our efforts to streamline our VST manufacturing platform, enabling the generation of clinical grade VSTs with specificity for AdV, CMV, EBV, BK virus and HHV6. In this editorial we will briefly describe the innovations that allowed the production of this broad spectrum anti-viral product and discuss the potential for extending this approach beyond the HSCT setting.

Generation and administration of broad spectrum VSTs

A particular clinical challenge when considering developing immune-based therapies for HSCT recipients is the requirement for the provision of protective immunity against not one, but multiple viruses. Our previous donor-derived VSTs were generated using conventional T cell manufacturing strategies, which relied on live virus/viral vectors as a source of antigenic stimulation, thereby limiting the number of viruses that could be simultaneously targeted to three viruses due to antigenic competition between different viral components (14). Thus, to achieve our goal of targeting not just EBV, CMV and AdV but also BK and HHV6 with a single VST line we had to substantially modify our *in vitro* manufacturing technology. We: (I) replaced virus/vector components with clinical grade overlapping peptide libraries spanning immunogenic antigens from each of our 5 target viruses; (II) mitigated the impact of antigenic competition by supplementing our cultures with the cytokines IL-4 + IL-7 (15), and (III) simplified and streamlined our VST production by utilizing G-Rex devices to reduce T cell apoptosis and enhance *in vitro* expansion (16). Thus, within 10 days we could reproducibly expand polyclonal [$CD4^+$ (57%±2%) and $CD8^+$ (35%±2%), n=48] T cell lines specific for up to 12 immunogenic antigens from our five target viruses. However, specificity was dependent on donor serostatus. For example, only 26 of our 48 donors were CMV seropositive and thus only these 26 lines contained a CMV-reactive T cell component while none of the lines generated from CMV seronegative donors recognized CMV. Overall, of the 48 lines generated, 14 had activity against all 5 stimulating viruses (pentavalent), 9 recognized 4 viruses (tetravalent), 12 were trivalent, 11 were divalent, and 1 was monovalent.

When these broad spectrum VSTs were infused to 11 allogeneic HSCT recipients between days 38 and 139 post-transplant there were no immediate infusion-related toxicities and only 1 patient developed *de novo* GvHD of the skin (grade II), which improved with the administration of topical steroids, highlighting the safety of these rapidly-generated broad spectrum VSTs. Three subjects received the cells prophylactically and all remained virus-infection free for greater than 3 months following infusion while eight patients were treated for a total of 18 viral infections/reactivations—2 for a single virus (AdV and BK, respectively), 3 for 2 viruses (CMV + BK; EBV + BK; EBV + BK), 2 for 3 viruses (CMV + EBV + BK; EBV + BK + HHV6) and 1 subject received treatment for 4 viruses (CMV + EBV + BK + HHV6). Remarkably, all 5 viruses proved sensitive to our adoptively-transferred VSTs, which produced a 94% response rate (15 complete and 2 partial responses) including in 4 patients with confirmed tissue disease [3 with BK-hemorrhagic cystitis and 1 with EBV-post-transplant lymphoproliferative disease (EBV-PTLD)]. In all cases viral clearance was associated with an increase in the frequency of T cells directed against the infecting virus(es). This study is still on-going and continues to demonstrate clinical benefit in the absence of toxicity, despite the short (10 days) manufacturing process.

Third party VST banks

Despite substantial improvements in *in vitro* manufacturing technology, the ability to provide allogeneic HSCT recipients with anti-viral protection using rapidly-generated donor-derived adoptively transferred T cells is contingent on prior donor exposure to the relevant pathogens, as previously outlined. Though the feasibility of generating and infusing VST populations from virus-naïve donors was recently demonstrated by Hanley and colleagues (17) the manufacturing procedure was complex, requiring multiple antigenic stimulations using adenovector-transduced dendritic cells and pepmix-pulsed EBV-transformed lymphoblastoid cell lines (EBV-LCL), and time consuming (approx. 4-6 weeks for EBV-LCL generation and 2-3 weeks for T cell production), hindering widespread application.

An alternative approach involves the preparation of banks of closely HLA-matched VSTs from healthy seropositive donors, which are available as "off the shelf" products for immediate use. However, there are theoretical concerns with this approach including the risk of GvHD, given that the majority of infused lines are mismatched at 1 or more HLA alleles. Similarly, the high degree of HLA mismatch may also lead to host rejection of the infused VSTs, resulting in transient antiviral activity. Nevertheless, a limited number of clinical studies have shown the promise of this strategy. For example, the group from Memorial Sloan Kettering administered third party EBV-specific T cells to five HSCT recipients with rituximab-resistant EBV PTLD and achieved complete responses in four without evidence of GvHD (18). Interestingly, the only non-responder had an EBV lymphoma of donor origin that escaped immune elimination following administration of a VST line with EBV-specific activity mediated through a non-shared allele. More recently, our group investigated whether the benefit of third party VSTs could be extended beyond the treatment of EBV-associated diseases. Using our conventional manufacturing process, we generated 32 trivirus specific T cell lines from healthy donors against EBV, CMV and AdV. Eighteen of these lines were used to treat 50 allogeneic HSCT recipients with drug-refractory infections [CMV (n=23), AdV (n=18), and EBV-PTLD (n=9)], with the lines for infusion based both on overall level of HLA match as well as confirmed anti-viral activity mediated through a shared HLA allele(s). Although the HLA matching between lines and recipient was low (between 1/6 to 4/6 alleles), the cells proved safe *in vivo* and produced complete or partial responses in 74% of patients infused (74% for CMV, 78% for AdV and 67% for EBV), the majority of which were durable (19).

Finally, to ask if our rapidly-generated broad spectrum VSTs could also provide anti-viral benefit when administered to third party recipients we developed a large bank (>55 lines) from healthy donors with activity against CMV, AdV, EBV, BK and/or HHV6, which we are currently infusing to patients with drug-refractory infections in an on-going Phase II clinical trial (NCT02108522). We have reported on the first 11 patients infused (Tzannou *et al*, ASGCT abstract, 2015) who received lines that were matched at 3/10 to 6/10 HLA alleles. Nine patients were treated for a single viral infection (CMV n=6; BK n=2; EBV n=1), and 2 patients had dual infections (BKV + EBV n=1; CMV + AdV n=1). Only one patient developed *de novo* grade 1 GvHD of the skin 4 weeks post-infusion, which resolved with topical steroid use and another patient had a flare of chronic GvHD of the skin, coinciding with tapering of immunosuppression. Overall, we achieved partial or complete virologic responses in all patients infused, including in 2 with BK-associated hemorrhagic cystitis who experienced marked symptomatic improvement and

resolution of hematuria post-VSTs. This study is ongoing but preliminary results support both the safety and clinical benefit associated with administering rapidly-generated healthy donor-derived VSTs as an "off the shelf" product to patients with drug-refractory CMV, AdV, EBV, BK or HHV6 infections.

Extending T cell therapy beyond the HSCT setting

Given the rapid availability and apparent safety of third party VSTs in HSCT recipients with drug-refractory viral infections the natural extension is to consider if there are other immunocompromised patient populations that would similarly benefit from this therapy. In this section we discuss the potential for utilizing "off the shelf" VSTs as anti-viral therapy in patients with primary immunodeficiencies as well as recipients of solid organ transplants (SOT).

Patients with primary immunodeficiencies

Primary immunodeficiency disorders (PIDD) comprise a large group of congenital defects of immunity with heterogeneous features that increase susceptibility to common community pathogens, opportunistic infections, autoimmune and allergic diseases (20). Among PIDDs with impaired or absent T cell function, such as severe combined immunodeficiency (SCID), infections associated with CMV, EBV, AdV, Varicella Zoster virus (VZV) and a range of respiratory viruses are frequent and lead to significant morbidity and mortality (21-23). Adoptive therapy with VSTs in this scenario might provide a safe and effective means of controlling viral disease in the short term—in essence providing a viable bridge therapy to enable patients advance to a curative stem cell transplant. To date, "off the shelf" VSTs have not been utilized in this setting but at our center two patients with EBV infections (viremia) received autologous EBV-specific T cells, which in one patient resulted in resolution and long term viral control. In the other patient, EBV viremia persisted but this patient was successfully transplanted 4 years later and subsequently received stem cell donor-derived VSTs, leading to viral clearance (24). Though the potential utility of third party VSTs has yet to be explored it represents an exciting avenue to pursue to improve clinical outcomes in this vulnerable population.

Solid organ transplant (SOT) recipients

The intensity and long-term requirement for immunosuppression to prevent allograft rejection pre-disposes SOT recipients to a wide range of viral complications, particularly within the first year of transplant (25). Many of the same viruses that afflict HSCT recipients (such as CMV and BK virus) also account for a spectrum of clinical diseases in SOT recipients including, importantly, allograft dysfunction (26,27). Aside from the previously mentioned general limitations of antiviral drugs, in the SOT setting their use may be further restricted due to renal dysfunction that is prevalent in 10-90% of SOT recipients (28,29), highlighting the attractiveness of "off the shelf" VSTs as a therapeutic option. However, an important consideration when considering applying VST therapies in the SOT setting is the fact that the majority of patients receive life-long immunosuppression to prevent allograft rejection, which additionally may compromise *in vivo* VST persistence and anti-viral function. The most frequently utilized are the calcineurin inhibitors cyclosporin A and FK506, which exert their immunosuppressive function by binding to cyclophilin (CyPA) and FK-binding protein 12 (FKBP-12), respectively. These complexes inhibit the calcium-sensitive phosphatase CN from binding to the transcription factor nuclear factor of activated T cells (NFAT), thus preventing activation of cytokine genes in T cells (30). Consistent with this mechanism of action, Egli and colleagues demonstrated that *in vitro* exposure of CMV and BK virus-specific T cells to both agents impaired effector cytokine production (31,32) and Cosio *et al.* reported an elevated incidence of BK-nephropathy in their center when target FK506 trough levels at months 4 to 12 post-transplant were in the higher range of 8-10 ng/mL compared to 6-8 ng/mL (33).

One approach to render adoptively-transferred VSTs resistant to the adverse effects associated with calcineurin inhibitors is via genetic modification—an approach that has been pre-clinically investigated in a number of laboratories. For example, De Angelis and colleagues knocked down FKBP12 in EBV-VSTs using a small-interference RNA (siRNA) and demonstrated that in the presence of FK506, the "protected" cells exhibited enhanced proliferation and increased IFNγ production in response to EBV-derived peptides relative to their non-modified VST counterparts (34). This translated to better tumor control in mice engrafted with an EBV-positive lymphoma receiving FK506 intraperitoneally 3 times a week. Similarly, Ricciardelli *et al.* retrovirally modified EBV-specific T cells with a calcineurin A mutant (CNA12), which prevented docking of FK506/FKBP12 and cyclosporin A/CyPA complexes to calcineurin, and demonstrated that adoptively-transferred genetically modified cells could persist, localize and completely eradicate

tumor in a human B cell lymphoma mouse model, despite physiologic concentrations of FK506 (35). However, while both of these studies have demonstrated the feasibility of conferring resistance of immunosuppressive drugs via genetic engineering approaches, their clinical efficacy has yet to be tested.

An alternative strategy, which has been clinically applied, is the tapering of immunosuppression to allow for adoptive transfer of VSTs. Indeed, Haque and colleagues conducted a phase II multicenter trial in which third party EBV-specific VSTs (matched at 2 to 5 HLA alleles) were administered to 31 SOT (heart n=2; kidney n=13; liver n=10; liver and small bowel n=3; lung n=2; heart and lung n=1) and 2 HSCT recipients all of whom had refractory EBV-PTLD and whose immunosuppression had been tapered per individual center protocol (36). The majority of patients (n=23) received 4 infusions of cells (at 2×10^6 VSTs/kg) while 1 patient received 6 and 2 received 8 infusions. Nevertheless, despite the multiple infusions there were neither infusion-related reactions nor adverse effects on the allograft and allo-antibodies detected against mismatched HLA alleles were detected in just a single patient. Importantly, the study showed response rates of 64% and 52% at 5 weeks and 6 months, respectively, with a statistically significant trend towards a better outcome with closer HLA matching and higher percentage of infused $CD4^+$ T cells. A follow-up study by the same group reported similar clinical benefit in 5 SOT recipients (kidney n=1; heart n=2; liver n=1; kidney and heart n=1) with EBV-PTLD following the adoptive transfer of third party EBV-specific T cells matched at 3/10 to 9/10 HLA antigens, with complete responses achieved in 4 of 5 patients treated (37). The non-responding patient was a cardiac transplant recipient treated for EBV-associated non-hematopoietic sarcoma and received haploidentical VSTs (generated from the father), which produced a partial regression of the lesions as measured by radiological imaging. Nevertheless, the patient subsequently died from infection. CMV has also been targeted using third party VSTs. Macesic and colleagues published a case report regarding a patient with persistent ganciclovir-resistant CMV viremia who had become dialysis-dependent due to thrombotic microangiopathy of his renal allograft (38). Further attempts to improve his persistent viremia involved tacrolimus discontinuation and prednisone tapering followed by a single infusion of a 3/6 HLA-matched CMV-specific T cell line (1.6×10^7 VSTs/m^2). Post-infusion the patient developed a mild fever but no other adverse effects were noted and within 4 months his CMV viral load decreased from $>5\times10^6$ copies to 682 copies/mL and remained controlled up to 1 year.

Thus, early clinical data using predominantly third party EBV-specific T cells, supports the extension of third party VSTs to the SOT setting, particularly in patients whose immunosuppression can be tapered to tolerable levels without compromising the allograft.

Future perspectives

In the future, it is likely that VSTs will become an increasingly important means of providing safe and effective anti-viral protection to immune compromised patients. In addition, we can consider further extending the breadth of our products to include emerging viruses such as HHV7, human metapneumovirus, coronavirus, and bocavirus, should prospective studies identify them as causative factors in post-transplant morbidity and mortality (39,40). Ultimately, for this approach to be used as a standard of care, extension beyond academic centers will be required as will the performance of randomized controlled clinical trials. However, given the strides in improving VST manufacturing, the extension to a broad range of viruses, and the clinical benefit mediated by cells administered as an "off the shelf" product we are closer than ever before to achieving our goal of providing VST therapy as a front line anti-viral modality to immune compromised patients.

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Footnote

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