Primary T cells expressing chimeric receptors specific for tumor or viral antigens have considerable therapeutic potential. Unfortunately, their clinical value is limited by their rapid loss of function and failure to expand in vivo, presumably due to the lack of costimulatory molecules on tumor cells and the inherent limitations of signaling exclusively through the chimeric receptor. Epstein-Barr virus (EBV) infection of B lymphocytes is near universal in humans and stimulates high levels of EBV-specific helper and cytotoxic T cells, which persist indefinitely. Our clinical studies have shown that EBV-specific T cells generated in vitro will expand, persist, and function for more than 6 years in vivo. We now report that EBV-specific (but not primary) T cells transduced with tumor-specific chimeric receptor genes can be expanded and maintained long-term in the presence of EBV-infected B cells. They recognize EBV-infected targets through their conventional T-cell receptor and tumor targets through their chimeric receptors. They efficiently lyse both. EBV-specific T cells expressing chimeric antitumor receptors may represent a new source of effector cells that would persist and function long-term after their transfer to cancer patients. (Blood. 2002;99:2009-2016)
MD, the hybridoma cell line 14.G2a (mouse IgG2a-k)17 was provided by Ralph A. Reisfeld (La Jolla, CA), and anti-14.G2a idiotypic antibody 1A718 (TriGem) by Titan Pharmaceuticals (South San Francisco, CA). The LMP-2/HLA-A2 tetramer (HLA-A-0201/CLGGLLMV) (single letter amino acid codes) was obtained from the MHC Tetramer Core Facility (Atlanta, GA).

Construction of chimeric receptor genes

The variable domains of monoclonal antibody 14.G2a were cloned as single-chain Fv (scFv) molecules into the replicative form of fUSE5 vector phage DNA.19 G D2-binding phages were selected by immunoscreening with enzyme-linked immunosorbent assay (ELISA). Chimeric chain receptor genes were assembled using pRSG-γ.1 The human γ chain transmembrane and cytoplasmic portions were amplified from pGEM3z19,20 A truncated receptor was engineered by polymerase chain reaction (PCR) by inserting a stop codon after the first 3 cytoplasmic amino acids. The chimeric genes were subcloned into the BamHI and NcoI sites of the retroviral vector SFG13 (provided by R. C. Mulligan, Cambridge, MA).

Production of recombinant retrovirus

Fresh retroviral supernatants collected from transiently transduced Phoenix-eco cells were used to infect the packaging cell line PG13 in the presence of polybrene (8 μg/mL) twice for 48 hours at 32°C. Viral supernatants were generated on the resulting bulk producer cell lines for 24 hours at 32°C.

Generation of EBV-transformed B cell lines

Peripheral blood-derived mononuclear cells (5 × 10⁶) were incubated with 10 μL concentrated supernatant from the EBV-producer cell line B95-8 in a total of 200 μL medium for 30 minutes. The cells were then plated at 10⁶ cells/well in a flat-bottomed 96-well plate in RPMI 1640 medium (Gibco BRL, Gaithersburg, MD) containing 10% fetal calf serum (FCS; HyClone; Logan, UT), and 2 mM L-glutamine (Pharmingen, San Diego, CA) at 37°C. After 24 hours, the supernatants were harvested and analyzed for human interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL-4, IL-10, and IL-12 (Pharmingen) or granulocyte-macrophage colony-stimulating factor (GM-CSF; R & D Systems, Minneapolis, MN) by ELISA according to the manufacturer’s instructions.

Cytotoxicity assays

Cytotoxic specificity was determined in standard ⁵¹Cr release assays. Various numbers of T-effector cells were cocultivated in triplicate with 5000 target cells labeled with 100 μCi (3.7 MBq) ⁵¹Cr in a total volume of 200 μL in a V-bottomed 96-well plate. After 4 hours of culture at 37°C and 5% CO₂, the supernatants were harvested, and radioactivity was counted in a gamma counter. Maximum release was determined by lysis of target cells with Triton X. To determine HLA class I or II restriction of cytolytic activity, target cells were preincubated for 30 minutes with 16.5 μg/mL W6/32 or CR3/43 antibodies (Dako, Carpinteria, CA). For cold target inhibition assays, unlabeled inhibitor cells (cold targets) were seeded in plates at various cold-to-hot target ratios. Effector cells were then added and incubated for 30 minutes at 37°C before labeled target cells (hot targets) were added.

Proliferation assays

Transduced T lymphocytes were cocultivated in triplicate at 5 × 10⁶ cells/well with various tumor cell targets or autologous or allogeneic EBV-LCLs at a 4:1 stimulator-to-responder ratio. Following a 72-hour coculture period, wells were pulsed with 2.5 μCi (0.0925 MBq) [³H]-thymidine for 18 hours, and the samples were harvested onto glass fiber filter paper for β-scintillation counting.

Results

Transduced EBV-specific CTLs express the chimeric receptor while maintaining their immunophenotype

Eight EBV-specific CTL lines, generated from 4 different seropositive healthy donors13,14 were transduced with 14.G2a-γ chimeric receptor genes. This receptor is derived from the 14.G2a monoclonal antibody that recognizes Gp350, a ganglioside antigen present on tumors of neural crest origin,17,22 including neuroblastoma and small cell lung cancer, as well as glioblastoma and melanoma. Flow cytometric analysis of CTLs stained with anti-14.G2a idiotype-specific antibody identified chimeric receptors on 10.2% to 43.1% of the CTLs (mean, 16.5%). Chimeric receptor expression was maintained over the entire period of culture (up to 45 days) without any apparent down-regulation. CD4⁺ and CD8⁺ T lymphocytes within the cultured cell population were transduced equally well (Figure 1).

After 3 stimulations with autologous LCLs, the majority of the CTL lines had a characteristic immunophenotype12,13: CD3⁺CD4⁻ on 80% to more than 90% of the cells and CD3⁺CD4⁺ T-cell helper on 4% to 21%. Fewer than 5% of the cells showed an immunophenotype characteristic of natural killer (NK) cells (CD3⁻CD16⁺CD56⁻). One cell line was predominantly CD3⁺CD4⁺. Transduction of CTLs did not result in any changes of cellular immunophenotypes by comparison with nontransduced
cells (not shown). Hence, introduction and expression of the chimeric receptor does not shift the phenotype of EBV-specific CTLs from that known to be able to expand, persist, and induce tumor regression following infusion in vivo.12-15

Triggering of the native T-cell receptor but not the \( \zeta \) chimera induces proliferation and expansion of modified EBV-specific CTLs

To confirm that signaling through the chimeric receptor alone provides a proliferation stimulus insufficient for in vitro expansion of the cells, we cultured 14.G2a-\( \zeta \) transduced and nontransduced EBV-CTLs in the presence of LCLs, irradiated GD2 (LAN-2), and GD2 (A-204) tumor cell targets and rhIL-2 (40 IU/mL), or EBV-CTLs alone. Incubation with the tumor targets did not elicit a proliferative response from either the modified or unmodified cells, as demonstrated by \( [3 \text{H}] \)-thymidine incorporation (Figure 2A). In contrast, autologous LCLs triggered substantial \( [3 \text{H}] \)-thymidine uptake by both types of CTL lines. Furthermore, whereas transduced CTLs continued to expand in response to stimulation with irradiated autologous LCLs, with kinetics similar to those of nontransduced cells, the transduced CTLs could not be maintained in culture for longer than 4 weeks when stimulated with tumor cells alone (Figure 2B). These results are compatible with in vivo data showing that chimeric receptor stimulation alone is inadequate to maintain T-cell proliferation and expansion.8,9

Chimeric receptor-modified CTLs specifically release cytokines in response to autologous EBV and GD2 tumor targets

Having demonstrated that chimeric EBV-specific T cells could be readily expanded ex vivo, we next compared functional activation of transduced EBV-specific CTLs by their native T-cell receptor and chimeric receptor-defined cellular targets. We determined the pattern of cytokine release by modified T lymphocytes after incubation with GD2 and GD2 tumor target cells, as well as with autologous EBV-infected LCLs.

Coculture with tumor cells does not result in CTL lysis or growth inhibition

To exclude the possibility that coculture with GD2 tumor cells is toxic to T cells independent of chimeric receptor triggering, we performed control experiments by testing the cytotoxicity of GD2 tumor cells toward chimeric receptor-transduced CTLs in standard \( ^{51} \text{Cr} \) release assays, and by comparing the expansion of CTLs in the presence of EBV and tumor targets.

The EBV-specific CTLs were not susceptible to cytolysis by JF or LAN-1 tumor cells after coincubation periods of up to 18 hours (not shown). Furthermore, CTL expansion was not decreased in the presence of tumor cells, when compared to allogeneic LCLs or absence of stimulator cells, indicating that the tumor cells did not actively inhibit CTL expansion (not shown).
The CTL cultures containing 5% to 15% 14.G2a-ζ-transduced T lymphocytes released IFN-γ (up to 2982 pg/mL) and GM-CSF (up to 1278 pg/mL) during coincubation with tumor target cells at a 3:1 target-to-effector ratio for 24 hours. Numbers above columns indicate the amount of cytokine secretion in response to autologous LCL targets for each population. Data shown are representative of independent experiments performed with CTL lines from 3 donors.

The cytolytic specificities of nontransduced and transduced cells were compared in standard 4-hour 51Cr release assays (Table 1). Following transduction, the CTLs had received at least 1 and up to 4 further weekly stimulations with autologous EBV targets before cytotoxic activity was assessed. The corresponding nontransduced CTLs had received an equal number of restimulations. At an effector-to-target ratio of 40:1, the percentage of autologous LCL targets lysed by nontransduced CTL lines ranged from 27% to 81% (mean, 49.6%), including one CTL line with a high percentage of CD4+ T cells. After transduction with chimeric receptor genes, 30% to 66% (mean, 47.6%) of autologous LCL targets were lysed by these lines. Under the same conditions, only 5% to 23% (mean, 10.1%) of HLA-mismatched EBV-transformed targets were lysed by nontransduced CTLs, compared with 3% to 19% (mean, 6.7%) by 14.G2a-ζ-transduced cells. None of the lines had discernible activity against autologous phytohemagglutinin-stimulated lymphoblasts. Whereas nontransduced CTLs were incapable of lysing tumor targets (0%-5%), 21% to 50% (mean, 36.6%) of GD2- transduced tumor cells were lysed during coincubation with 14.G2a-ζ-transduced CTLs. No cytolytic activity of transduced cells against the Gd2 tumor target A-204 was seen. The specificity of the interaction with the GD2-expressing tumor cell targets was further confirmed by preincubation of Gd2 tumor targets with 14.G2a monoclonal antibody, resulting in up to 81% inhibition of lysis by 14.G2a-ζ-transduced cells (not shown). The cytolytic activity of cell lines tested for up to 29 days after transduction (4 stimulations) was comparable to that of lines tested over shorter intervals. Retesting of a CTL line after an additional round of restimulation with autologous LCLs resulted in comparable cytolytic activity against both EBV and tumor targets (Table 1).

Figure 4 compares the cytolytic activities of 3 different 14.2a-ζ-transduced CTL lines against EBV and tumor cell targets. The chimeric receptor-bearing T cells recognized and lysed GD2 tumor cells (LAN-1) and autologous LCLs with similar efficiency over the entire range of effector-to-target ratios, but responded poorly to Gd2 tumor cells (A-204). Inhibition studies with anti-MHC antibodies identified MHC class I as the major restriction element for LCL lysis by nontransduced and 14.G2a-ζ-transduced CD8+ CTL lines. However, preincubation with HLA class I and II blocking antibodies did not affect the lysis of LAN-1 target cells, indicating a lack of MHC restriction (Figure 5). These results establish that the EBV-specific chimeric T cells kill their tumor target cells.

### Table 1. Cytolytic characteristics of EBV-specific CTLs with or without chimeric receptors

<table>
<thead>
<tr>
<th>CTL line</th>
<th>Nontransduced</th>
<th>14.G2a-ζ transduced</th>
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<tr>
<td></td>
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</tr>
<tr>
<td>10†</td>
<td>81</td>
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*Effector-to-target ratio 40:1.
†CTL line 5, retested after additional restimulation with autologous EBV-LCL.
EBV targets through their (MHC-restricted) conventional receptor, and their tumor targets through the (MHC-unrestricted) chimeric receptor.

14.G2a-ζ-transduced EBV-specific CTLs have functional specificity for both EBV and tumor antigens

Because of the superior in vivo functional capabilities of EBV-specific cell lines over single epitope specific clones, the preceding studies were performed on mixed populations of CTLs.

Therefore to demonstrate that transduced populations of EBV-specific CTLs are functionally bispecific for the native T-cell receptor antigen and the chimeric receptor target, rather than recognizing such targets independently of one another, we performed cold target inhibition assays. The antigen specificity of both tumor cell and LCL lysis by gene-modified EBV-specific CTL lines was determined by analyzing the capacity of unlabeled autologous LCLs and GD2 tumor cells to block lysis of tumor cells and LCLs, respectively. Although lysis of the GD2 tumor target LAN-1 by 14.G2a-ζ-transduced EBV-specific CTLs was HLA independent, it could be inhibited by addition of nonlabeled EBV target cells, whereas lysis of EBV+ targets could be diminished by competition from nonlabeled tumor cells (Figure 6).

As an additional demonstration of coexpression of the T-cell receptor, specific for an EBV-encoded antigen, as well as the chimeric receptor on individual cells within the CTL culture population, we costained a transduced CTL line from an HLA-A2 donor with LMP-2 specific tetramers and with anti-14.G2a-idiotype antibody 1A7 (Figure 7). Slightly more than 7% of the cells specific for LMP-2 had detectable levels of 14.G2a-ζ surface expression, comparable to the bulk CTL population, which contained 5.8% 1A7+ CTLs. Taken together, our functional observations from cold target inhibition experiments as well as the receptor coexpression studies provide evidence that the same population of cells is responsible for killing both EBV and tumor targets, and that this effect is associated with coexpression of EBV-specific and tumor-specific receptors on the same cells.

Chimeric receptor-modified CTLs are rescued to proliferate by stimulation with autologous EBV-LCLs

The clinical success of transduced EBV-CTLs will likely depend in part on these cells being able to proliferate when restimulated by autologous EBV targets following exposure to tumor cells. We therefore compared the proliferative responses of the CTLs to tumor targets and to EBV targets after repeated stimulation with either autologous LCLs, allogeneic LCLs, GD2 tumor cells, or GD2 tumor cells, and in the absence of stimulation. Confirming our previous data, autologous LCLs alone were capable of inducing the

Figure 4. Cytolytic activity of 3 EBV-specific CTL lines against EBV and tumor targets. Transduced CTLs were tested against 51Cr-labeled autologous LCLs, class I mismatched allogeneic LCLs, GD2 neuroblastoma tumor cells (LAN-1), G2t rhabdo-myosarcoma cells (A-204), or autologous phytohemagglutinin-stimulated lymphoblasts. (A) 14.G2a-ζ and 14.G2a-δ-transduced CTL line no. 2, (B) 14.G2a-ζ-transduced CTL line no. 4, (C) 14.G2a-ζ-transduced CTL line no. 8.

Figure 5. Lack of MHC restriction in chRec-mediated tumor cell killing by transduced CTLs. 51Cr-labeled GD2 LAN-5 neuroblastoma cells and autologous EBV-LCLs were preincubated for 30 minutes with monoclonal antibodies recognizing monomorphic determinants of HLA class I or HLA class II, then coincubated for 4 hours with 14.G2a-ζ-transduced CTL at a 20:1 effector-to-target ratio.
effector cells to proliferate above their low background level. However, CTL exposed to tumor cells for 1 to 2 weeks still showed a strong proliferative response when restimulated with autologous LCLs, comparable to the response obtained in cells receiving weekly stimulations with EBV targets (Figure 8).

Discussion

Adoptive immunotherapy with chimeric receptor-modified T lymphocytes has shown promise in preclinical studies as a means to combat infectious and malignant diseases. However, the first clinical evaluation of chimeric receptor-modified cells revealed a disappointing lack of correlation between in vivo and in vitro cytotoxicity. One of the major factors limiting successful therapeutic use of modified T cells is their failure to expand and their short life span in vivo, even in the absence of any immune response directed against the chimeric T cells. CD4\(^{+}\) helper function plays a crucial role in establishing or maintaining CD8\(^{+}\) CTL-mediated antiviral or antitumoral immunity, and long-term maintenance of engineered T cells is clearly improved if both CD8\(^{+}\) and CD4\(^{+}\) transduced T cells are infused, rather than CD8 cells alone. Previous clinical trials in human immunodeficiency virus (HIV) infection have demonstrated prolonged, high-level persistence of chimeric receptor-modified CD4\(^{+}\) and CD8\(^{+}\) T cells for at least 1 year. However, no significant mean change in plasma HIV RNA or blood proviral DNA was observed in patients with persisting modified T lymphocytes. No analysis of in vivo function of modified T cells over time has been conducted in this study. An explanation for this observation is that even in the continued presence of detectable chimeric receptor-modified cells in vivo, the

Figure 6. Cold target inhibition assay. 14.G2a-\(\zeta\)-transduced EBV-specific CTLs were preincubated with unlabeled autologous LCL (Auto-LCL), HLA-mismatched allogeneic LCL (Allo LCL), GD2 (LAN-1), or GD2 (A-204) tumor cells at various cold-to-hot target ratios. Cytotoxic activity was then determined against \(^5\)Cr-labeled autologous LCL (A) and GD2 LAN-1 tumor cells (B) at an effector-to-target ratio of 40:1.

Figure 7. LMP-2/HLA-A2 tetramer\(^{+}\) CTLs coexpress the 14.G2a-\(\zeta\) chimeric receptor. On day 14 after transduction, CTLs were stained with monoclonal antibody IA7 and FITC-labeled goat antimouse antibody, then incubated with PE-labeled LMP-2/HLA-A2 tetramer, followed by staining with PerCP-labeled anti-CD8 antibody. One million events were acquired and analyzed. Indicated are the absolute numbers of events for tetramer-positive cells that express detectable levels of 14.G2a-\(\zeta\) in a population of nontransduced CTLs (A) or 14.G2a-\(\zeta\)-transduced CTLs (B).

Figure 8. Transduced cells are rescued to proliferate by stimulation with autologous EBV-LCLs. 14.G2a-\(\zeta\)-transduced (A) and nontransduced (B) EBV-specific CTLs were stimulated with irradiated autologous (Auto) or mismatched allogeneic (Allo) LCLs, or with GD2 (LAN-1) or GD2 (A-204) tumor cells at a 1:4 stimulator-to-responder ratio. After 7 to 14 days, CTLs were stimulated with autologous LCLs (Auto/Auto, LAN-1/Auto, JF/Auto, A-204/Auto, Allo/Auto) or stimulated as before (LAN-1/LAN-1, JF/JF, A-204/A-204, Allo/Allo). Proliferative responses were then assessed by measurement of [\(\text{H}\)]-thymidine uptake. Shown is a representative experiment of 2.
surviving T lymphocytes may lose their ability to produce cytokines and to lyse their targets, reflecting functional inactivation of the modified cells. Supporting this concept are studies in a transgenic mouse model that showed that chimeric receptor-mediated signaling was not sufficient to trigger activation of resting primary T cells. Although the lack of coreceptor signaling by most tumor targets probably contributes to this effect, it is also likely that chimeric receptors provide only limited access to downstream signaling pathways. The pattern of T-cell activation triggered by chimeric receptor engagement that we observed in our study, including efficient target cell lysis, reduced levels of specific cytokine release, and lack of cellular proliferation, is reminiscent of the T-cell response to altered peptide ligands as a consequence of incomplete phosphorylation of TCR-associated proximal activation motifs.

Taken together, the above results indicate that efficient and sustained expansion and activation of transduced chimeric effector T lymphocytes in vivo will require (1) T-cell helper activity provided in a cognate fashion, (2) signaling through the native TCR/CD3 complex, and (3) the presence of costimulatory signals and cytokines. Our results suggest that the introduction of chimeric receptors into ex vivo–generated EBV-specific T-cell lines will meet all of these requirements (Figure 9). These cell lines contain antigen-specific CD4+ helper T cells that contribute to immune control of EBV latency by providing growth factors capable of maintaining both CD4+ and CD8+ cells, as well as CD8+ cytotoxic T cells. The target cells are EBV+ B lymphocytes, which present antigens extremely well. They express both class I and class II MHC-restricted antigenic epitopes, facilitating cognate interactions between CD4+ and CD8+ T cells, and are rich in costimulator molecule expression.

What is the evidence that the properties of such T-cell lines will be reiterated in vivo? In patients given gene-marked EBV-specific CTLs, we can detect a high degree of in vivo expansion, resulting in long-term persistence and antiviral activity for more than 6 years. Expression of chimeric receptor genes in EBV-specific CTLs does not interfere with the ability of the cells to proliferate or to respond to autologous EBV-infected targets (Figure 2A,B). Their ability to kill tumor cell targets through the chimeric receptor is retained even after expansion driven through the EBV-antigen specific native receptors (Table 1, Figure 4). Following exposure to tumor cells in culture, transduced CTLs can be rescued to proliferate and expand by stimulation through their EBV-specific receptor (Figure 8). In our system, none of the tumor cell targets proved toxic to the CTLs or inhibitory to their expansion. We therefore postulate that as a result of the continued presence of viral antigens in an EBV-infected host, engineered antitumor T lymphocytes with native specificity for EBV antigens will survive for extended periods. Such an effect can result only if the same T cell is both EBV and tumor specific, a requirement that was met in the present study, both phenotypically (as demonstrated by fluorescent analysis with an anti-idiotype monoclonal antibody and an EBV tetramer) and functionally (as shown by cross-inhibition of each target cell with either EBV-infected B lymphocytes or tumor cells). Although cross-inhibition can be demonstrated in short-term assays in vitro, it should not prove a significant limitation in vivo because a single T cell can kill multiple cellular targets sequentially, disengaging from each once killing has been achieved. This effect is illustrated by the ability of chimeric EBV-CTLs that have been repeatedly stimulated by EBV-LCLs, to subsequently kill tumor targets (Figure 3). Hence, after infusion of chimeric EBV-specific T cells into EBV+ individuals, there should be lifelong in vivo restimulation via the native T-cell receptor in the presence of adequate costimulation as illustrated in Figure 6. This will prevent functional inactivation of the cells and should enable them to continuously lyse any chimeric receptor target cells they encounter.

Without performing a clinical study, we cannot be certain that there will be sufficient stimulation by EBV antigens in vivo to produce expansion and maintenance of chimeric T cells at a sufficient level to produce antitumor effects. Nonetheless, recent evidence from our current adoptive transfer studies of EBV CTLs suggests that expansion and functional maintenance of these cells will occur even in patients with “normal” levels of EBV DNA and without evident EBV+ malignancy (C.R. and Barbara Savoldo, unpublished observations, August 2001). This effect is probably a consequence of periodic reactivation of EBV (and other herpesviruses). Serologic evidence suggests that reactivation after primary infection is a frequent event, and recent measures of serum EBV-DNA levels have produced similar results. Should the number of functionally activated EBV-specific CTLs and their level of activation in the absence of massive EBV reactivation prove to be too low to provide a stimulus of sufficient strength for chimeric-mediated tumor cell lysis, it may prove possible to boost T-cell responses by immunization with autologous irradiated LCLs.

In principle, the above strategy may be used for any tumor target to which a chimeric receptor can be made. However, one of the major advantages of chimeric T cell–based therapies is that they obviate the need to select and expand the scanty tumor-specific T cells present in the circulation. The EBV-specific CTL chimeras we describe here would seem to remove that advantage, because an antigen-specific selection and expansion process will be required after all. But, in practical terms, the expansion of EBV CTLs and the expansion of tumor-specific CTLs are quite separate propositions. The high frequency of EBV-specific precursor cells in peripheral blood and the excellent antigen-presenting capacity of EBV-infected B cells makes this a robust system. Over the past 6 years, we have successfully generated EBV-specific CTL lines from 138 of 140 donors, including cancer patients pretreated with chemotherapy. More than 100 patients with EBV-associated infections or malignancy have received EBV-CTL infusions with no serious adverse effects. These results have been confirmed by
others. Moreover, because the infused cells are expected to expand markedly in vivo and persist in the circulation for extended periods, only limited numbers of cells may need to be grown and infused. The use of EBV-specific cell lines is to be preferred to the use of clones because (1) they are simpler to prepare, (2) the combination of CD4+ and CD8+ cells present produces a more sustained immune response than CD8+ clones alone, and (3) EBV antigen escape mutants are less likely to arise. Because high-efficiency cotransfection was achieved with cultures containing up to 90% nontransduced CTLs, there would be no need to coexpress marker or selection genes—a major source of immunogenicity after chimeric T-lymphocyte infusion. The individual components of this proposed system have already been safely used in humans; the chimeric receptor in the form of monoclonal antibodies administered to patients with malignancy, and the EBV-CTLs given to patients at risk of EBV-lymphoma or with Hodgkin disease. Our findings suggest that combining these components as antitumor chimeric receptors expressed by EBV-specific T cells may overcome many of the current limitations of chimeric T-cell immunotherapy.

References

Epstein-Barr virus–specific human T lymphocytes expressing antitumor chimeric T-cell receptors: potential for improved immunotherapy

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