Editor's Summary

Standing the Test of Time

Retroviral vectors were once the mainstay of gene transfer because they could stably integrate into the host genome. However, some patients in early trials developed leukemia because of insertional mutagenesis. Now, Scholler et al. report that retroviral vector–mediated gene transfer in T cells may not have the same safety concerns, and that these cells may persist over a decade in patients.

The authors followed patients from three clinical trials who received T cells transduced with gammaretroviruses carrying a chimeric antigen receptor. They found that these cells were present in recipients over a decade after infusion at levels higher than those induced by standard vaccines. These cells were still functional, had stable levels of engraftment, and did not require host immunosuppression before transplant. Moreover, the authors found no evidence of integration-induced immortalization, with no observable enrichment of integration sites near genes involved in growth control or transformation. Thus, the safety of retroviral vectors may be cell type–specific, opening up engineered T cells as a delivery platform for therapeutics.

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Decade-Long Safety and Function of Retroviral-Modified Chimeric Antigen Receptor T Cells

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The success of adoptive T cell gene transfer for treatment of cancer and HIV is predicated on generating a response that is both durable and safe. We report long-term results from three clinical trials to evaluate gammaretroviral vector–engineered T cells for HIV. The vector encoded a chimeric antigen receptor (CAR) composed of CD4 linked to the CD3ζ signaling chain (CD4ζ). CAR T cells were detected in 98% of samples tested for at least 11 years after infusion at frequencies that exceeded average T cell levels after most vaccine approaches. The CD4ζ transgene retained expression and function. There was no evidence of vector-induced immortalization of cells; integration site distributions showed no evidence of persistent clonal expansion or enrichment for integration sites near genes implicated in growth control or transformation. The CD4ζ T cells had stable levels of engraftment, with decay half-lives that exceeded 16 years, in marked contrast to previous trials testing engineered T cells. These findings indicate that host immunosuppression before T cell transfer is not required to achieve long-term persistence of gene-modified T cells. Further, our results emphasize the safety of T cells modified by retroviral gene transfer in clinical application, as measured in >500 patient-years of follow-up. Thus, previous safety issues with integrating viral vectors are hematopoietic stem cell or transgene intrinsic, and not a general feature of retroviral vectors. Engineered T cells are a promising form of synthetic biology for long-term delivery of protein-based therapeutics. These results provide a framework to guide the therapy of a wide spectrum of human diseases.

INTRODUCTION

Retroviral vectors have been associated with safety concerns in clinical applications (1). For example, when individuals with X-linked severe combined immunodeficiency (SCID-X1) were treated by gene transfer to restore the missing interleukin-2 (IL-2) receptor γ (IL2RG) gene to hematopoietic stem cells using gammaretroviral vectors, although 9 of 10 patients were successfully treated, 4 of the 9 developed T cell leukemia several years after gene therapy (2). Similarly, a lentiviral vector encoding β-globin flanked by insulator elements has been used to treat β-thalassemia successfully in one human subject. However, a clonal expansion was observed after integration in the HMGAC2 locus, raising concerns regarding the long-term safety of this approach (1). Thus, a key concern with the potential use of retroviral vectors has been whether expansion of cells harboring vectors integrated near genes involved in growth control will inevitably result in clonal proliferation or whether the safety concerns are cell type–specific.

Adoptive transfer therapies are often further limited by a requirement for host lymphodepletion before T cell transfer (3). Until recently, persistence of gene-modified T cells in the absence of a strong selective advantage has been modest. However, in children with congenital immunodeficiency, persistence of gene-corrected lymphocytes has been detected for at least 12 years (4). Similarly, in lymphopenic patients after hematopoietic stem cell transplantation, gene-marked Epstein-Barr virus (EBV)–specific cytotoxic T lymphocytes have been shown to persist for up to 9 years (5).

The study reported here was undertaken as part of long-term follow-up for gene transfer studies using integrating vectors as mandated by the U.S. Food and Drug Administration (FDA) (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm). T cells expressing CD4ζ become activated upon binding HIV gp120 envelope protein on infected cells (6, 7). Between 1998 and 2005, three clinical studies evaluated the CD4ζ CAR (chimeric antigen receptor) expressed in autologous CD4+ and CD8+ T cells in subjects with active viremia (8) or in T cell–reconstituted patients with chronic HIV-1 infection [clinicaltrials.gov NCT01013415 and (9)]. See the Supplementary Materials for protocol information, including other variables that were tested across the trials including dose and dose schedule, and the effect of IL-2 administration on cell persistence.

RESULTS

Greater than 16-year half-life of CD4ζ CAR T cells after infusion

To assess the durability of gene marking, we analyzed total genomic DNA (gDNA) from peripheral blood mononuclear cell (PBMC) samples from 43 subjects collected between 1 and 11 years after infusion by quantitative polymerase chain reaction (qPCR) for CD4ζ.
Stable engraftment was observed in 212 of 221 subject samples (Fig. 1A). Most of the subjects had an average CD4ζ frequency in PBMCs of 0.01 to 0.1%, with some exceeding 0.1% (Fig. 1, B to D). Linear mixed-effects modeling (10) was used to measure their decay rates, and their disappearance half-life (t_{1/2}) was >16 years for the three trials (Table 1), suggesting that CD4ζ-modified T cells may persist for decades. The extrapolation beyond year 9 is subject to the unknown biology of whether decay remains linear after year 9. In contrast, persistence of gene-modified T cells has been modest in previous trials involving patients with cancer and HIV, with decay half-lives of less than 30 days.

Decade-long expression and function of the CD4ζ CAR transgene

Gene silencing of integrating vectors is a potential limitation of retroviral gene therapy (11). To interrogate expression of CD4ζ, we isolated total RNA from 13 subjects 2 to 10 years after infusion and measured transcriptional activity by reverse transcription–PCR (RT-PCR) for CD4ζ. All but two samples (the samples with lowest detectable engraftment) had measurable CD4ζ RNA (Fig. 2A) at levels that significantly correlated with DNA copies (table S1). This indicates ongoing transcription of CD4ζ for at least 10 years after infusion of gene-modified T cells.

We then evaluated whether the CD4ζ CAR was expressed and functional. CD4ζ-positive cells could not be sorted for functional testing by standard methods such as cell surface staining and cytokine release because of (i) limiting numbers of cells in annual samples, (ii) the inability to phenotypically distinguish native CD4 from CD4ζ, and (iii) CD4 expression by natural CD8 cells upon activation (12). Therefore, we developed an assay to enrich CD4ζ cells in response to ligation of CD4ζ using artificial antigen-presenting cells (Fig. 2B and fig. S1A). We evaluated cryopreserved PBMC samples obtained 3 to 7 years after infusion. In seven of nine subjects, the proportion of the CD4ζ copies after stimulation showed a 3- to 13-fold increase in prev-

![Figure 1](https://www.sciencemag.org/content/48/132ra53/suppl/DC1)

**Fig. 1.** Persistence of CD4ζ-modified CAR T cells over 11 years after infusion. (A) Total samples tested at annual visits and the corresponding number of samples with detectable CD4ζ. (B to D) Persistence of CAR T cells for the 43 individual patients in the (B) Mitsuyasu, (C) Deeks, and (D) Aronson trials at annual visits beginning at 1 year after infusion. The limit of detection (LOD) for the assay is plotted as a dotted reference line.

**Table 1.** Decay rates and half-lives of engrafted CD4ζ cells in subjects on the three clinical protocols. Limit of quantification is 26.6/1 x 10⁶ or 1.42 copies on log₁₀ scale; see Fig. 1 for data points. Note that although the estimated half-life and time to reach limit of detection (LOD) are listed as years after infusion, they were calculated using the estimated cell count beginning at year 1 (or year 2 for Mitsuyasu study because of limitation in sample availability in year 1) rather than the actual initial infusion cell counts. In this analysis, there was on average 25 independent patients available (minimum, 10 patients) for estimating the rate of decline at each time point through year 9. CI, confidence interval.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects in follow-up</th>
<th>Average number of follow-up samples evaluated per patient</th>
<th>Decay rate (log₁₀ copies/year)</th>
<th>Half-life (years after infusion)</th>
<th>Years to reach LOD</th>
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<td></td>
<td></td>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
</tr>
<tr>
<td>Deeks</td>
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<td>5.4</td>
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<td>−0.115 to −0.006</td>
<td>24.5</td>
</tr>
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<td>Mitsuyasu</td>
<td>17</td>
<td>4.9</td>
<td>−0.085</td>
<td>−0.145 to −0.025</td>
<td>16.5</td>
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<tr>
<td>Aronson</td>
<td>9</td>
<td>5</td>
<td>−0.112</td>
<td>−0.200 to −0.023</td>
<td>17.5</td>
</tr>
<tr>
<td>Combined</td>
<td>43</td>
<td>5.3</td>
<td>−0.074</td>
<td>−0.107 to −0.041</td>
<td>24.2</td>
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<td>9.2–42.5</td>
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<td>12.3–98.3</td>
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Designation at the bottom with the subject ID and year after infusion of the sample.

Numbers were evaluated from the gDNA of subject PBMCs before and after activation by qPCR analysis.

CD4 copy number was measured as the relative increase in the average copy number of CD4 presenting cells expressing the high-affinity Fc receptor CD64 (KT64) and 100 IU of IL-2. CD4 mRNA. GAPDH is expressed at a high level, so that greater expression of CD4 abundance is to count the number of integration sites from the infused cell product available in sufficient quantities, using ligation-mediated PCR and Mu-1 disruption of gene regulation. These unique integration sites were determined from the infused cell product and post-infusion PBMCs (table S2).

We first examined the global integration site pattern relative to genomic features such as gene density, gene expression, and CpG islands. For comparison, we also analyzed integration sites from SCID-X1 gene therapy in stem cells (16). These represent candidates for genes involved in clonal expansion or persistence. However, we did not find evidence for enrichment (table S4). Because gammaretroviruses integrate near gene promoters, we also compared the frequency of integration near the 5′ ends of cancer-related genes in the preinfusion gene-modified T cell product and post-infusion samples. We failed to detect significant enrichment over time (Fig. 3B).

Retroviral gene transfer safety record in >500 patient-years of observation

The stable level of engraftment with a functional transgene combined with the maturity of the clinical trials provides a unique opportunity to determine the safety and durability of gene transfer with integrating vectors. Clinical monitoring of the patients at yearly intervals has not detected any suspected or documented occurrences of hematologic disorders suggestive of retroviral genotoxicity. The clinical data set represents more than 540 patient-years without integration-mediated toxicity. Therefore, on the basis of a Poisson distribution assumption, we are 95% confident that the true adverse event rate is
Integration site analysis of CD4ζ-modified CAR T cells. (A) Longitudinal abundance and dynamics of CD4ζ-modified T cells. The top left corner of each panel shows the patient number. qPCR measurements of total CD4ζ copy number per million PBMCs are shown longitudinally for individual subjects (blue line). The x axis shows months after infusion, and the y axis shows qPCR vector copy number. Stacked bar graphs are shown above time points where integration sites were isolated and depict the relative abundance of integration sites on the proportion of sequence reads detected using Mse I and Tsp 509I. The top five abundant sites are differentially colored, with all other less abundant sites colored gray. The total number of unique sites detected at a given time point is shown above the corresponding bar graph. (B) Frequency of integration near cancer-associated gene 5′ ends. Integration sites were separated into four bins with one bin for preinfusion sites and three bins for post-infusion sites (x axis). The percent of sites found within 50 kb from a gene 5′ end that were also within 50 kb from a cancer-associated gene’s 5′ end are shown (y axis). The number of sites <50 kb from a gene’s 5′ end is shown at the top of each bin. No significant difference between the preinfusion and the post-infusion bins was found in pairwise comparisons using Fisher’s exact tests.

It is likely that mature human T cells are somewhat resistant to insertional genotoxicity, consistent with the known resistance of mature mouse T cells to transformation (29). In contrast, mature B cells do not appear to have this resistance to transformation (30). A poten-

less than 0.0068 per person-year or, equivalently, no more than one event in every ~147 years.

DISCUSSION

The safety of gene transfer with retroviral vectors has been difficult to establish because of a paucity of studies with persistently high levels of gene-modified cells. The persistence of gene-modified T cells has been modest in previous trials involving patients with cancer and HIV, with decay half-lives of less than 30 days (18–27). Considering the large number of subjects analyzed in this study and the extent of marking [T cells with more than 2 × 10¹¹ integration events were infused in the trials, and the human genome consists of about 3 × 10⁹ base pairs (bp)], it is likely that most targets in the human genome hosted vector integration. Thus, the absence of adverse events and clonal expansion is unexpected; previous estimates predict 10⁻⁵ to 10⁻⁸ adverse events per retrovirus insertion event (28).
tial mechanism for observations that mature T cells appear to offer “safe harbor” to integration events that is unlike B cells—where homeostasis is regulated at the population level—the homeostasis of T cell mass is asserted at the clonal level by mechanisms involving intraclonal competition (31, 32). The essentially stable persistence of CD4ζCAR T cells that we have observed is similar to the 14-year half-life reported for vaccinia-specific human T cells (33). The notion of homeostatic regulation of CD4ζ T cells at the clonal level is consistent with the previous demonstration that CAR T cells continue to express their natural T cell receptors (TCRs) (6).

The mechanisms responsible for the high-level persistence of CD4ζ CARs likely include the use of improved cell culture technology that promotes central memory cells (34), a nonimmunogenic transgene, and signaling from the CD4ζCAR moiety. The decay rates of CD4ζ-modified T cells in the peripheral blood suggest that persistence could last decades. One possible mechanism for long-term persistence in this study could be repetitive CAR stimulation as a result of periodic encounters with HIV envelope (35). Alternatively, binding of the extracellular CD4 portion of the CD4ζ chimeric CD4ζCAR with its low-affinity ligand, major histocompatibility complex (MHC) class II, might lead to signaling through the ζ chain to promote persistence (36). Both are supported by findings that ζ T cell persistence is enhanced by TCR signals to self-ligands (37).

One limitation of the present study is that it is not yet possible to determine the survival rates of the CAR T cells in this study beyond 9 years because of limited numbers of samples. The predicted decay rate is based on modeling that assumes continued linear decay rates that were observed during the initial 9 years. Another caveat is that the clinical safety that we have observed may be specific for T cells and is CD4ζζ, whether similar safety could be obtained in other cell types is unknown.

In addition to the safety features of CD4ζ CAR cells, an important clinical implication of our results is that the patients did not require conditioning with lymphoablative regimens to achieve stable engraftment; lymphoablation has been necessary with stem cell therapies and for T cell engraftment in cancer patients. The safety and long-term persistence of engineered T cells provides a further rationale for cell-based HIV eradication strategies (38). Furthermore, these findings provide a framework for the design of long-term gene delivery strategies for genetic disorders and other benign conditions where chemotherapy is not feasible.

**MATERIALS AND METHODS**

**Clinical protocols**

Each of the three CD4ζ trials had unique therapeutic protocols in antiretroviral drug (ARV)-treated HIV subjects. The Mitsuysa study (8) was a phase 2 open-label trial, infusing a single dose of $2 \times 10^{10}$ to $3 \times 10^{10}$ CD4 and CD8 T cells per subject with detectable HIV loads divided into two groups: (i) those that received $6 \times 10^8$ U of IL-2 continuously infused over 4 days beginning 4 hours before T cell infusion or (ii) those that received no IL-2. The Deeks study (9) was a phase 2 clinical trial treating ARV-controlled HIV subjects [levels near limits of detection (LODs)], and $1 \times 10^{10}$ CD4/CD8 cells were infused three times 2 weeks apart. Subjects were enrolled onto a cohort of (i) those receiving CD4ζ-modified T cells or (ii) those receiving only unmodified T cells. The Aronson study (clinicaltrials.gov NCT01013415) was a randomized, three-cohort trial of subjects with ARV-controlled HIV infections (levels below detection). Two cohorts received infusions of $8 \times 10^8$ to $9 \times 10^8$ CD4ζ-modified CD4/8 T cells with or without subcutaneous injections of IL-2 (1.2 mIU/m² per day) for 56 days. The third cohort group received IL-2 only. For each of these studies, subjects were intensely monitored and evaluated after infusion in the first year for clinical responses, safety, and correlative effects. This report was initially undertaken as part of the FDA-mandated long-term follow-up for monitoring for delayed adverse events in patients receiving gene therapy using integrating vectors. Under this requirement, subjects participated in annual laboratory and physical exams up to 15 years after infusion. The collection of frozen PBMCs from the annual visits for each subject in each of the studies was compiled. The completeness of each subject’s annual visit follow-up profile was primarily determined by the subject’s compliance with protocol-specified study visits and to adequate specimen quality.

**Determination of CD4ζ copy numbers**

A qPCR assay was developed to detect the amplicon formed by the CD4ζ and ζ chimeric gDNA for qPCR was isolated from frozen pellets of $1 \times 10^8$ PBMCs obtained from the buffy coat of processed blood from subject annual visits with QIAamp DNA Micro Kit (Qiagen). qPCR was performed in 20-µl volumes with the 384-well format on ABI HT7900. Validated CD4ζ and huGAPDH (human glyceraldehyde-3-phosphate dehydrogenase) primer/probe sets were used to quantify respective copy numbers of subject samples from standard curves. Assay results were evaluated by ABI’s SDS2.3, Excel, and SigmaPlot software. To determine the average CD4ζ copies/1 $\times 10^8$ PBMCs, CD4ζ copy numbers were determined with four replicates of 250 ng of gDNA, and GAPDH copy numbers were determined with three replicates of 50 ng of gDNA and then used to normalize the CD4ζ copies to $1 \times 10^8$ cells with the following formula: $2 \times (CD4ζ$ copies/GAPDH copies) $\times 1 \times 10^8$. TaqMan qPCR assay performance criterion is as follows: limit of quantification (LOQ) is about one copy in 7600 cells, LOD is about one copy in 38,000 cells, positive control within 80% of expected value, and $R^2$ must be greater than 0.995.

**Determination of CD4ζ decay slopes and half-life**

A linear mixed-effects model (10) with the time since infusion as an independent variable was used to estimate the rate of CD4ζ decay from year 1 to year 9 after infusion. Using both random intercepts and random slopes, we modeled potential correlation among repeated measurements over time and between-subject variability in the initial values, as well as the rate of decay. For the combined data, the difference between studies in the year 1 cell counts was adjusted by including indicator variables of individual study in the model as covariates.

**RT-PCR of CD4ζ subject samples**

Cryopreserved subject PBMCs were thawed and allowed to recover overnight before total RNA was isolated with Qiagen RNeasy Plus kit. The RNA was reverse-transcribed with mixed hexamers and evaluated by TaqMan analysis for the detection of CD4ζ and the reference gene huGAPDH. A resulting positive $C_t$ value for CD4ζ was then subtracted from the $C_t$ value of the GAPDH to determine $\Delta C_t$ of CD4ζ relative to GAPDH. As a control for CD4ζ DNA contamination, an RT reaction without the reverse transcriptase was done for each sample. A negative signal was found in all control samples, indicating that samples
had no contaminating DNA. The two samples with undetectable CD4ξ mRNA described in Fig. 2A also had transgene copy numbers below 100, suggesting that 0.01% of CD4ξ-modified T cells in PBMCs may be the limit to detect CD4ξ RNA by this RT-TaqMan procedure.

**Integration site recovery and analysis**

Purified gDNA was digested with Mse I, Tsp 509I, or for Mu-mediated recovery (13), with Ban I. Samples with limiting DNA amounts were whole genome–amplified with the illustra GenomiPhi V2 DNA Amplification Kit (GE Healthcare) before digestion. PCR adapters were installed by T4 ligase or Mu transposase. Mse I and Tsp 509I samples were then digested again with Msc I to prevent recovery of vector sequence. Nested PCR was performed with conditions described previously (15) and primers specific to the CD4ξ vector LTR. Amplification products were purified with AmPure beads and sequenced with 454 pyrophosphate sequencing technology (39). Genomic sequences aligning within 3 bp of the LTR end and showing unique best alignments to the human genome by BLAT (hg18, version 36.1, >98% match score) were considered true integration sites. Comparisons to genomic features were performed as described previously (40, 41) with Fisher’s exact tests, $\chi^2$, or a combination of conditional logit, regression, and Bayesian model averaging. An explanation of supplementary genomic heatmaps can be found in Ocwieja et al. supplementary text “Guide to Interpreting Genomic Heat Maps Summarizing Integration Site Distributions” (42). Identification of cancer-related genes was done with a collection of cancer-related gene lists from seven different sources (http://microb230.med.upenn.edu/protocols/cancergenes.html). Integration site data sets and oligonucleotides used for analysis are listed in tables S5 and S6. The CD4ξ integration sites were compared to integration sites recovered from other studies that used gammaretroviral vectors in T cells (17) and hematopoietic stem cells (16).

**SUPPLEMENTARY MATERIALS**

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**Fig. S1. Development and validation of the K562 activation assay for functional testing of**

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