IMMUNOTHERAPY

Adoptive cellular therapy: A race to the finish line

Carl H. June,[1]* Stanley R. Riddell,[2]* Ton N. Schumacher[3]*

Adoptive T cell transfer for cancer, chronic infection, and autoimmunity is an emerging field that shows promise in recent trials. Using the principles of synthetic biology, advances in cell culture and genetic engineering have made it possible to generate human T cells that display desired specificities and enhanced functionalities compared with the natural immune system. The prospects for widespread availability of engineered T cells have changed dramatically, given the recent entry of the pharmaceutical industry to this arena. Here, we discuss some of the challenges—such as regulatory, cost, and manufacturing—and opportunities, including personalized gene-modified T cells, that face the field of adoptive cellular therapy.

INTRODUCTION

Adoptive cell transfer (ACT) is a term coined by Billingham and colleagues to describe the transfer of lymphocytes to mediate an effector function (*1*). Presently, there are three types of therapies that are advancing on a path toward regulatory approval (Fig. 1): tumor-infiltrating lymphocytes (TILs) as well as chimeric antigen receptor (CAR) and T cell receptor (TCR) engineered T cells. TILs have been developed with slow but continuing progress over several decades, primarily at the National Cancer Institute. Recently, an international phase 3 randomized trial began for treating patients with metastatic melanoma with TILs (NCT02278887). A number of pharmaceutical and newly formed biotechnology companies are now commercializing various forms of ACT, including TIL therapies (Table 1).

In contrast to TILs, gene-transfer–based strategies have been developed to overcome the consequences of immune tolerance on the tumor-specific T cell repertoire. These approaches redirect T cells to tissues by the transfer of CARs composed of antibody-binding domains fused to T cell signaling domains, or transfer of TCR α/β heterodimers. The infusion of gene-modified T cells directed to specific targets offers the possibility to endow the immune system with reactivities that are not naturally present and has the added benefit of the rapid onset of action that is usually seen with cytotoxic chemotherapy or with targeted therapies, contrasting to delayed effects observed with vaccines and some of the T cell checkpoint therapies.

Currently, most trials are using α/β T cells for ACT. However, investigators are exploring the use of numerous lymphocyte subsets—including γ/δ T cells, invariant natural killer (NK) T cells, NK cells, and T helper 17—for their specialized functions in various clinical settings of cancer and chronic infection. For indications involving autoimmunity, tolerance induction, prevention of organ graft rejection, and treatment of graft-versus-host disease (GVHD), regulatory T cells (T_{reg} cells), including natural and induced T_{reg} cells, are being tested. Myeloid-derived suppressor cells and regulatory B cells, which have anti-inflammatory properties involving mechanisms distinct from T_{reg} cells, have also been proposed as novel forms of ACT (*2*, *3*). In this Perspective, we review the status of ACT and the rapidly emerging role of the biotechnology industry in the race to accelerate the development and promote the widespread availability of this new form of cellular therapy that has demonstrated efficacy treating patients with refractory life-threatening cancers.

ACT is generally considered in the context of cancer, typically leukemias and melanoma (Table 1). It is interesting to note from a historical perspective that some of the first forms of ACT involving gene-modified T cells were conducted two decades previously in patients with advanced HIV-1/AIDS (*4*). Many of the results from trials conducted in patients with AIDS have informed current concepts in the field of cancer, as exemplified by the demonstration that CAR T cells could survive for more than a decade in HIV/AIDS patients (*5*). These initial trials were done in order to control drug-resistant forms of HIV-1 infection. However, the current challenge in the field is to develop cellular therapies with the potential to eliminate the reservoir of HIV-1 that is resistant to current antiviral therapies (*6*). The field has been energized by an extraordinary experiment conducted by Gero Hütter and colleagues in Berlin in a patient who has apparently been cured of HIV infection after an allogeneic hematopoietic stem cell transplant and ACT from a homozygous C-C chemokine receptor type 5 (CCR5) Δ32 donor (*7*). There are several approaches to induce a cell-intrinsic resistance to HIV-1 infection and to target the reservoir of HIV-1 by gene-modified ACT and cytotoxic T lymphocytes (CTL) (*8*, *9*).

Cancer immunotherapies that target T cell checkpoints, such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) (*10*), rely on the ability of the endogenous T cell compartment to recognize the tumor as foreign because of the epitopes it carries. TIL therapy likewise relies on an intrinsic tumor recognition capacity of the T cell compartment, and checkpoint therapies and TIL therapy may therefore be assumed to have potential for a similar set of human cancers. Notably, recent work suggests that T cell recognition of neoantigens that are created as a consequence of tumor-specific mutations forms a major component of the clinical activity of checkpoint therapies (*11*, *12*), and clinical activity of these therapies may therefore be highest in tumors with a high mutational load. Adoptive therapy with gene-modified T cells has the potential to address an entirely different need by creating a tumor-specific T cell compartment that is otherwise lacking in patients (Fig. 1). As such, gene-modified ACT has potential for tumor types that may not be responsive to T cell checkpoint or TIL therapies, such as most cancers occurring in children and many of the hematological malignancies. In addition, gene-modified ACT addresses a different critical node in the "cancer–immunity cycle," the series of stepwise events required for an anticancer immune response to lead to cancer cell eradication (*13*). Furthermore, T cell checkpoint therapies and gene-modified ACT have the potential to work synergistically.

[1]Center for Cellular Immunotherapies and the Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-5156, USA. [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA 98109, USA. [3]Division of Immunology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands.
*Corresponding author. E-mail: cjune@exchange.upenn.edu (C.H.J.); sriddell@fredhutch.org (S.R.R); t.schumacher@nki.nl (T.N.S.)

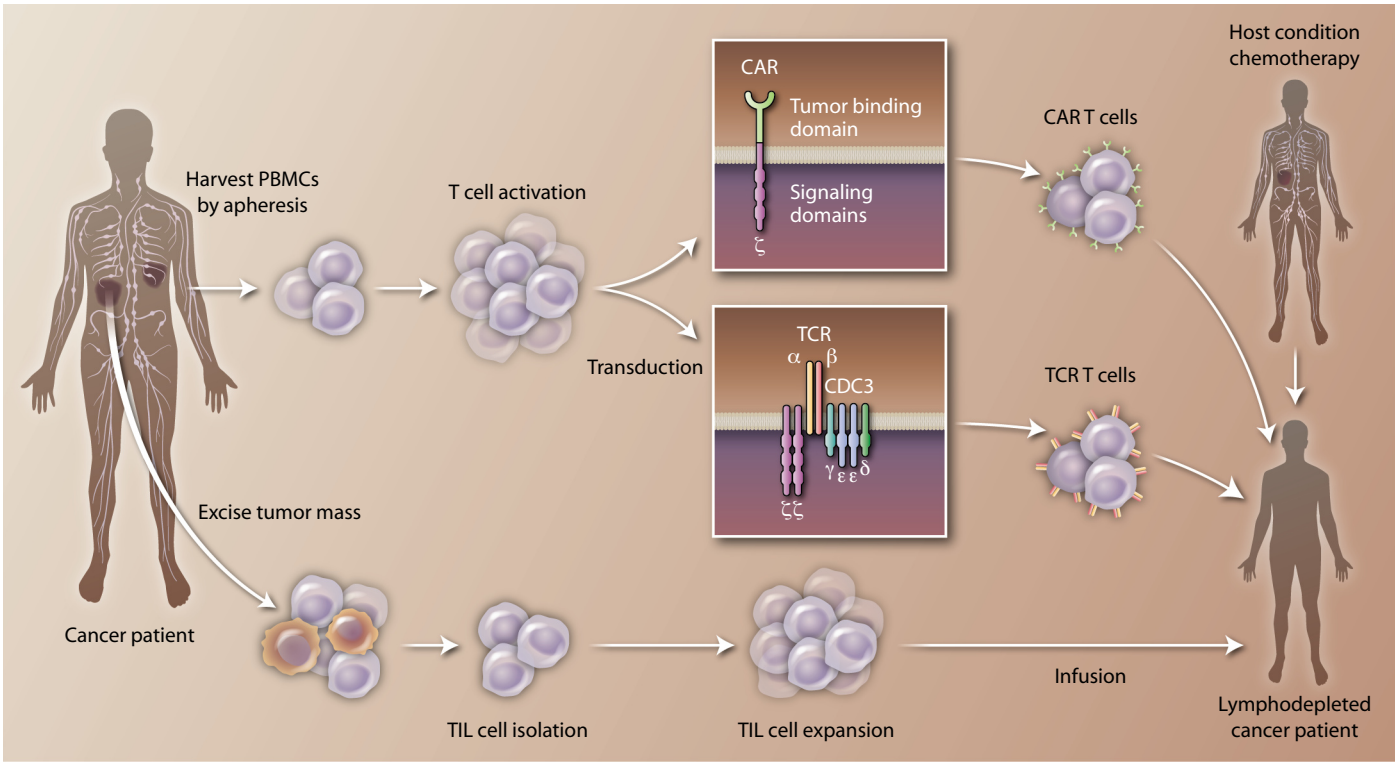

Fig. 1. Adoptive cell therapy is currently represented by three general approaches. TILs are produced after surgical excision of tumor and enrichment and expansion of TILs from a disaggregated tumor biopsy sample. TCR- and CAR-modified T cells are produced from peripheral blood lymphocytes in a manufacturing step that includes introduction of the desired receptor through viral or nonviral methods in order to engineer cells. Patients often receive a lymphodepleting chemotherapy regimen before infusion. PBMC, peripheral blood mononuclear cell.

SOURCE OF CARS AND TCRS

Most of the chimeric antigen receptors currently used to create gene-modified T cells are derived from mouse antibodies, and both antibody and T cell responses against CARs have been observed in clinical trials (*14*, *15*). Furthermore, the extent of this problem may presently be underestimated because the most visible trials in the area have involved the targeting of the B cell compartment—a clinical setting in which transgene-specific humoral immunity will be less of an issue than in settings in which the humoral immune system is left intact. To minimize the impact of transgene-specific immune responses on the activity of introduced cells, the use of humanized or fully human antibodies obtained from mice transgenic for the human immunoglobulin (Ig) loci forms an obvious solution. Clinical trials with fully human CARs have only recently opened (NCT02209376 and NCT01837602). In addition, it may be beneficial to engineer the CAR format so that the formation of nonhuman sequences at the domain fusion sites is also avoided.

By the same token, immunogenicity of nonhuman TCR sequences has been described in a subset of patients treated with TCR-modified T cells—in this case, involving antibody recognition of mouse TCR variable domains (*16*). Here again, the isolation of receptors from the human T cell repertoire or from mice that carry a humanized TCR repertoire is likely to be an effective solution (*17*). In the case of TCRs, the source from which the receptor is obtained will also influence the likelihood of off-target toxicity: the recognition and destruction of normal tissues that express a different epitope from that of the targeting agent. From a conceptual point of view, the T cell pool from a human lymphocyte antigen (HLA)–matched individual should be considered the safest source of TCRs, but the quality of the available TCR pool is likely capped by T cell tolerance for many antigens. The breadth of the available repertoire will be—roughly in order—greater in HLA-transgenic mice, in T cell pools from HLA-mismatched individuals, and in the in vitro TCR display systems that avoid T cell tolerance altogether. However, the safe use of the latter type of technologies is only feasible when rigorous assay systems are in place that can screen against unwanted cross-reactivity.

TOXICITY FROM ACT

In accord with expectations, toxicities from ACT have increased as the therapies have become more potent. Although TILs have generally been safe (as with other forms of autologous cellular therapy), both on-target and off-target recognition of normal tissue can occur with engineered T cells. For instance, on-target toxicity has been reported in patients treated with T cells engineered with a TCR that is specific for the carcinoembryonic antigen, resulting in severe inflammatory colitis developed from expression of target antigen in normal colon (*18*). With B cell–directed forms of ACT with CARs, commonly observed on-target toxicities have been B cell aplasia and cytokine release syndrome (*19*). Severe cardiac toxicity was reported owing to off-tumor and off-target recognition of titin after ACT with T cells expressing an affinity-engineered TCR that was originally specific for melanoma-associated antigen 3 (MAGE A3) (*20*). Methods involving computational and bio-

Table 1. Pharmaceutical and biotechnology companies in the ACT space. ACT applications are shown for cancers, infections, and GVHD.

Company	Technology/cell type	Indication
	Cancer	
Lion Biotechnologies	TIL (autologous)	Metastatic melanoma
Autolus	CAR (autologous)	Unspecified
Novartis	CAR (autologous) targeting CD19	Pediatric and adult ALL, diffuse large B cell lymphoma, non-Hodgkin's lymphoma (NHL)
Juno Therapeutics	CAR (autologous) targeting CD19, TCR (autologous) targeting Wilms tumor protein (WT-1)	Adult and pediatric ALL, NHL, adult acute myeloid leukemia (AML), non–small cell lung cancer (NSCLC)
Cardio3 Biosciences	CARs targeting NK cell p30-related protein (NKp30); NK group 2, member D (NKG2D); B7 homolog 6 (B7H6)	Range of hematological malignancies and solid tumors
Cellular Biomedicine Group	CARs targeting CD19, CD20, CD30, and EGFR	Range of hematological malignancies and solid tumors
CARsgen	CARs targeting glypican-3 (GPC-3)	Hepatocellular carcinoma
Celgene/Bluebird	CAR (autologous)	Range of hematological malignancies and solid tumors
Kite Pharma/Amgen	CAR (autologous) targeting CD19, TCR	Relapsed or refractory ALL
Cellectis/Servier/Pfizer	CAR (allogeneic, UCART 19)	CLL, ALL, and AML in preclinical stage, phase 1 for B cell leukemia to be initiated in 2015
GSK/Adaptimmune	TCR (autologous) targeting the cancer testis antigen NY-ESO-1 and other targets	Trials in multiple myeloma (MM), melanoma, sarcoma, and ovarian cancer
Janssen/Transposagen	CAR (allogeneic)	Unspecified
Unum Therapeutics/Sanofi-Genzyme	Antibody-coupled TCR (autologous)	Unspecified
Ziopharm Oncology/Intrexon	CAR	Unspecified
Opus Bio	CAR (autologous) targeting CD22	Pediatric and adult ALL and NHL, CD22 licensed to Juno
Takara Bio (Japan)	CAR (autologous) targeting CD19, TCR, MAGE-A4	NHL, esophageal cancer
Bellicum Pharmaceuticals	CAR (autologous) targeting CD19 with a proprietary safety switch to mute unwanted adverse events, such as cytokine release syndrome	Potential hematological malignancies and solid tumors
Cellular Therapeutics Ltd (UK)	CAR (autologous)	Metastatic melanoma, esophago-gastric cancer
Cell Medica (UK)	Virus-specific T cells (allogeneic) targeting Epstein-Barr virus antigen	Advanced NK/T cell lymphoma
Celdara Medical	CAR (autologous) targeting NKG2D	AML, advanced myelodysplastic syndrome (MDS), MM
Catapult Cell Therapy (UK)	TCR (autologous) targeting WT-1–overexpressing cells	AML, MDS
Medigene (Germany)	TCR (autologous)	Hematological malignancies
TheraVectys (France)	CARs (autologous) targeting CD19, CD33, and CD123	ALL, CLL, AML
BioNTech AG (Germany)	TCR, CAR (autologous)	Solid tumors (ovarian, endometrial, lung)
CARsgen (China)	CAR (autologous) targeting GPC-3 expressed in hepatocellular carcinoma; other CARs	Liver, lung, and brain cancers
FF CanVac	Virus-specific T cells (autologous)	Head and neck cancer
Apceth	Genetically engineered mesenchymal stem cells (MSC) (autologous)	Advanced, recurrent, or metastatic gastrointestinal cancer
Pocastem	Genetically engineered MSCs	Solid tumors (head and neck, brain)
TVAX Biomedical	Antigen-specific T cells (autologous)	Solid tumors (brain, kidney)
TC Biopharm (Scotland)	γ/δ T cells (autologous)	Melanoma
Immunovative Therapies (Israel)	Activated T cells (allogeneic)	Hematological malignancy, prostate cancer, breast cancer, glioblastoma, colorectal cancer with liver metastases, kidney cancer, NSCLC
CytoVac (Denmark)	Activated T cells/NK cells (autologous)	Glioblastoma, prostate cancer, pancreatic cancer
Conkwest	CAR NK cell line	AML
Coronado Biosciences	Activated NK cells (autologous)	AML
	HIV/Infection	
Calimmune	CCR5 knockdown $CD4^+$ T cells and stem cells	HIV
Cell Medica (UK)	Cytomegalovirus (CMV) infection after allogeneic hematopoietic stem cell transplant (HSCT)	CMV infection
Sangamo Biosciences	CCR5-mutated $CD4^+$ T cells and stem cells	HIV
Stage Therapeutics (Germany)	CMV-specific donor lymphocytes	CMV infection
Takara Bio (Japan)	mRNA interferase MazF (autologous) endoribonuclease–modified $CD4^+$ T cells	HIV
	GVHD	
Kiadis Pharma (Netherlands)	Allo-depleted T cells (allogeneic)	Facilitate early immune reconstitution without life-threatening (acute) GVHD in leukemia patients (ALL, AML, MDS) undergoing HSCT
Miltenyi Biotec GmbH/Prometheus Laboratories (Germany)	T_{reg}-enriched infusion (allogeneic) + low-dose IL2	Steroid-refractory chronic GVHD

logical approaches are being developed to predict off-target recognition by engineered TCRs (*21*).

Apart from toxicity consequent to the reactivity pattern of the introduced CAR or TCR itself, it is expected that autoimmunity and inflammation will sometimes result from the infusion of ex vivo–activated autologous lymphocytes. Current experimental trials exclude patients with active autoimmune disorders, so the incidence of immunopathology may rise when ACT achieves broad usage in the community. Severe side effects from CTLA-4 and PD-1 antagonism occur with relatively high frequency, especially upon combined checkpoint blockade (*22*, *23*), and we expect that this will occur with ACT unless, for example, steps are taken to edit out endogenous TCRs. In mice, the inflammatory consequences of immunotherapy are more severe in aged mice than in young mice and in obese rather than in thin mice (*24*). This may also happen in humans, and relevant to this is the observation that GVHD occurs more frequently and is more severe in aged rather than young patients (*25*).

A potential safety concern related to ACT with engineered T cells is integration-related insertional mutagenesis and cellular transformation—events previously demonstrated with engineered hematopoietic stem cells. To date, transformation of human lymphocytes has not been reported after ACT (*5*, *19*), and the incidence can be calculated to be less than one event per 1000 patient years of exposure to engineered T cells, an event rate that is lower than that reported for cytotoxic chemotherapy (*26*). The low genotoxicity with ACT may be due to cell-extrinsic mechanisms that control T cell homeostasis (*27*).

THE EXPANDING TOOLBOX FOR GENETIC ENGINEERING

Novel technologies that enable targeted alterations of the genome to modify or regulate cellular functions provide an opportunity for improving both the efficacy and safety of ACT. Zinc-finger nucleases (ZFNs) and transcription activator–like effector nucleases (TALENS) that rely on customized DNA binding proteins, and the natural bacterial CRISPR-Cas9 system of RNA-guided nucleases, can introduce DNA double-strand breaks at specific sites and lead to disruption of a gene sequence or provide a site for targeted gene insertion (*28*, *29*). ZFNs and TALENS have been used to disrupt endogenous TCR genes, and the first clinical application of ZFNs to disrupt expression of the HIV co-receptor CCR5 in $CD4^+$ T cells was reported recently (*30*–*33*).

Efficient genome editing paves the way for additional applications in ACT. The importance of T cell–intrinsic regulatory molecules such as CTLA-4 and PD-1 in suppressing beneficial tumor-reactive T cell responses has been established by using antibodies targeting these pathways (*34*–*36*). Selective editing of PD-1 or CTLA-4 genes in adoptively transferred T cells might similarly enhance efficacy without the side effects of systemic antibody blockade. Other regulatory pathways that inhibit T cell function locally in the tumor microenvironment have been revealed by introducing pooled short hairpin RNA (shRNA) libraries into tumor-specific T cells used in ACT, and this provides previously unidentified targets for gene editing, including intracellular targets that are not amenable to antibody-mediated blockade (*37*). A potential caveat of editing regulatory genes in T cells is that these molecules serve context-dependent roles in normal physiology, and permanent disruption, even in a subset of T cells, may have unforeseen consequences.

Genes can also be introduced into T cells in order to enhance their ability to localize at tumor sites and to function in the immunosuppressive tumor microenvironment. The introduction of chemokine receptor genes in T cells that bind chemokines produced by tumors can enhance T cell migration into tumors (*38*), and expression of dominant-negative transforming growth factor–β (TGF-β) receptors renders T cells resistant to the local inhibitory effects of TGF-β (*39*). Engineering T cells to secrete interleukin-12 (IL-12) induces a programmatic change in myeloid cells in the tumor microenvironment to promote tumor destruction, while avoiding the systemic toxicity of IL-12 (*40*).

Modifying T cells by means of gene editing or insertion to enhance therapeutic potency should coincide with attention to the safety of transferred T cells. Transgenes that provide for conditional cell suicide have been developed and can rapidly reverse acute or long-term toxicities of ACT. These include cell-surface molecules, such as CD20 or truncated epidermal growth factor receptor (EGFR), that are recognized by clinically approved monoclonal antibodies that mediate antibody-dependent cellular cytotoxicity (*41*, *42*). Herpes simplex virus thymidine kinase (HSV-TK) confers sensitivity of dividing T cells to ganciclovir and has been used effectively to eliminate transferred T cells that cause GVHD after allogeneic hematopoietic stem cell transplantation, although this approach is limited in immunocompetent hosts by immune responses to the viral TK (*43*). A nonimmunogenic suicide construct that consists of human caspase-9 fused to a modified domain of the human FK506-binding protein can induce cell death through exposure to a synthetic dimerizing drug, AP1903. The administration of AP1903 rapidly and completely reversed clinical manifestations of GVHD that occurred after T cell administration (*44*), suggesting that this "safety switch" approach may be sufficiently rapid to abrogate unexpected immediate toxicities of ACT.

FROM UNIVERSAL T CELLS TO PERSONALIZED ACT

Current approaches to gene-modified T cell therapy are personalized in the sense that a patient-specific cell product is created but generic in the sense that the same receptor is used for larger patient groups. As extensions to this, strategies to develop universal T cell products and to develop patient-specific receptors have recently been proposed.

Approaches toward universal T cell therapy aim to allow the widespread application of gene-modified T cell therapy at a lower cost (Fig. 2A). With respect to the creation of such universal T cells, several substantial barriers need to be overcome. First, alloreactivity within the endogenous TCR pool leads to GVHD when HLA-mismatched donor-derived T cells are used for therapy. By the same token, recognition of donor-cell allo-determinants by the patient's T cell pool leads to rapid rejection of infused cells unless additional measures are taken. Genome engineering technologies make it feasible to create T cell products in which one or both of the endogenous TCR chains have been inactivated, allowing a more comprehensive editing of T cell specificity and consequent avoidance of allo-reactivity (*30*, *31*, *33*). In addition, such inactivation of both the endogenous TCR α and β chains avoids the formation of the mixed TCR dimers that have been shown to cause GVHD in mouse models (*45*). With respect to technologies to suppress rejection of the infused cells, inactivation of donor major histocompatibility complex genes could potentially be used to prevent T cell–mediated rejection (*46*) but may at the same time trigger NK

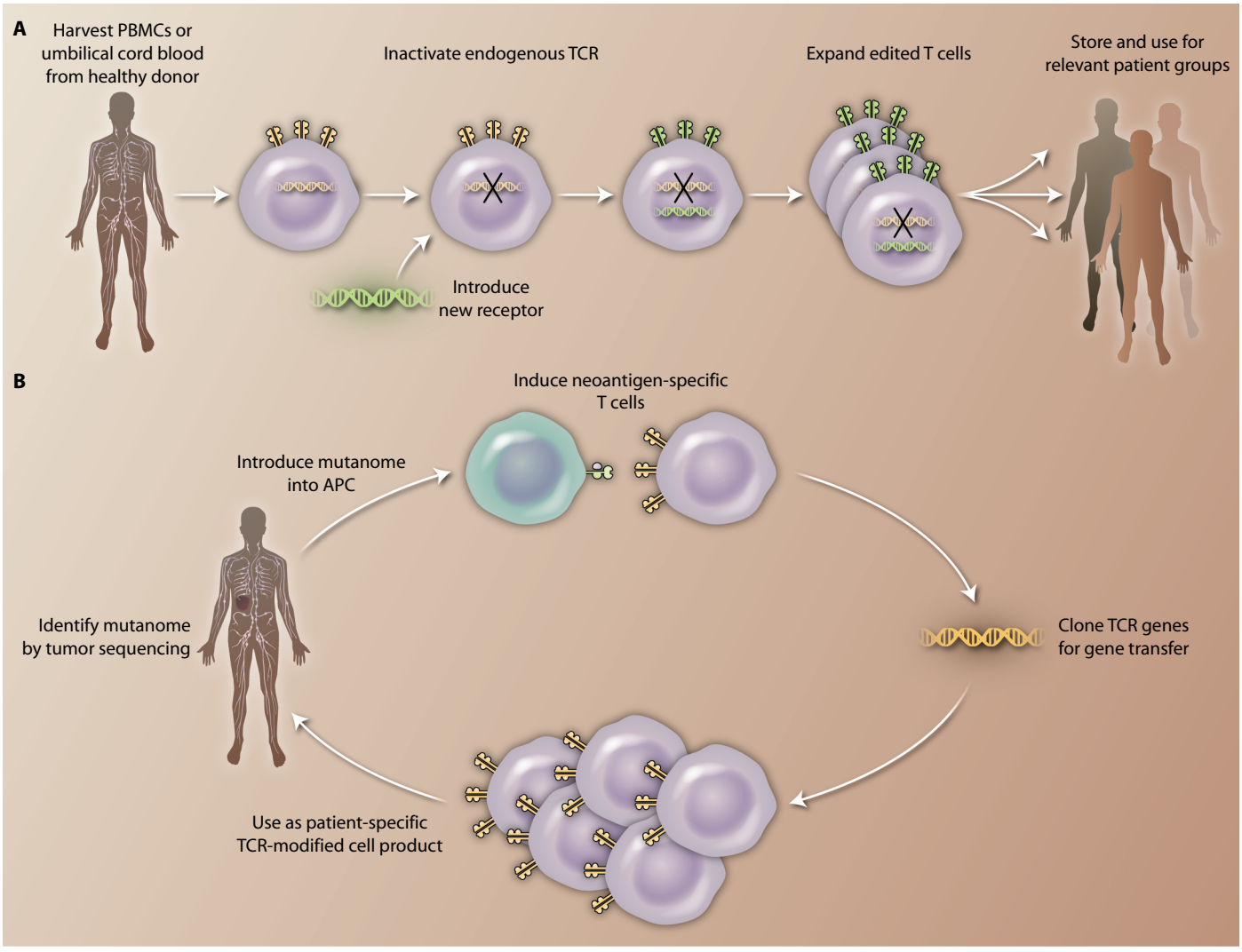

Fig. 2. From universal to highly personalized gene-modified ACT. (**A**) Universal T cells in which the endogenous TCR has been replaced by a CAR or TCR as "off-the-shelf" ACT products. Expression of the endogenous TCR can be eliminated through genetic editing. (**B**) Targeting the patient-specific mutanome by gene-modified ACT. Tumor-specific mutations are expressed in antigen-presenting cells (APCs), and the TCR repertoire is isolated from the responding T cells. The desired tumor-specific TCRs can be isolated and introduced into T cells for later ACT.

cell recognition. Conceivably, development of approaches that render infused cells selectively insensitive to immunosuppressive drugs may form a superior alternative.

At present, the number of antigens that can safely be targeted by TCRs or CARs is still limited to a handful. To increase the antigenic targets that are available to gene-modified T cell therapy, approaches to obtain receptors that are reactive against patient-specific neoantigens may be of interest (Fig. 2B). Recent work has shown that in human melanoma, both $CD8^+$ and $CD4^+$ T cell recognition of neoantigens occurs frequently (*11*, *47*, *48*). And based on overlap in mutational loads, formation of neoantigens that can be recognized by T cells can be expected in several other high-prevalence human tumors (*47*). In case the endogenous T cell pool generally "picks up" on the majority of neoantigens presented by an individual tumor, isolation of the relevant TCRs from the autologous T cell pool may be a way to boost immune reactivity against this class of antigens. Alternatively, it seems possible that in some human tumor types, priming of an endogenous T cell response may be inefficient. In such cases, it may be attractive to exploit antigen-presenting cells that express the patient-specific mutanome so as to induce such reactivities.

From a safety perspective, the targeting of the patient-specific neoantigen repertoire is highly appealing. However, it remains to be established for which tumor types neoantigen-specific TCRs can readily be obtained, and the logistic hurdles—with respect to regulation, timelines, and projected costs—are substantial.

TRANSLATIONAL BOTTLENECKS AND CHALLENGES

Therapeutically effective T cells can be derived from tumor infiltrates in melanoma patients; however, the peripheral blood is the preferable site for obtaining T cells for genetic modification for ACT because of the ease of procurement. To date, the focus has been on genetically modifying α/β T cells without regard to subset or differentiation status. However, α/β T cells are present in

functionally heterogeneous $CD4^+$ and $CD8^+$ subsets that differ in frequency, phenotype, transcriptional profile, and effector function. Current models suggests progressive differentiation from antigen-inexperienced naïve cells (T_N) to $CD62L^+$ central memory (T_{CM}), $CD62L^-$ effector memory (T_{EM}), and effector (T_E) T cell subsets, with loss of proliferative capacity and acquisition of effector function (*49*–*51*). Treatment efficacy after adoptive transfer of endogenous or genetically redirected tumor-reactive T cells correlates best with the ability of transferred T cells to proliferate and persist in vivo, suggesting that selection of T_N and/or T_{CM} may provide greater therapeutic potency. The optimal composition of $CD4^+$ and $CD8^+$ subsets for ACT may also differ depending on the malignancy being treated. Unfortunately, the lack of rapid, cost-effective, and efficient clinical-grade cell-selection devices and procedures currently impedes the evaluation of therapeutic T cell products derived from distinct T cell subsets.

A challenge for all cell therapies, including T cell therapy, is the need to develop cost-effective and efficient manufacturing and delivery capabilities. The sipuleucel-T (Provenge®) dendritic cell vaccine for prostate cancer developed by Dendreon demonstrated that cell therapies could be manufactured and delivered to physicians but illustrated that efficacy needed to be high to justify the cost and complexity and to compete with more easily administered pharmaceuticals. ACT has been pioneered in academic laboratories for which the resources to develop closed robotic automated systems for cell selections, genetic modification, and expansion are not readily available. The recent influx of biotechnology and pharmaceutical companies into cell-based therapeutics should accelerate automation to reduce cost and improve feasibility and delivery (Table 1). Off-the-shelf genetically modified tumor-specific T cells from allogeneic donors could further diminish the manufacturing burden for ACT, in case the immunologic barriers to this approach can be overcome.

The ability to redirect T cells with previously unidentified TCRs and CARs is increasing the types of malignancies that can be targeted with ACT. In the case of CARs, few targets that are exclusively expressed by tumor cells have been identified. The potential for—and consequences of—on-target recognition of normal cells can be evaluated in animal models, providing that the expression patterns are identical to humans (*52*). Logic gates, such as dual targeting with split receptor systems, may be used to improve the selectivity of tumor cell recognition by CAR-T cells for targets expressed on tumor and a subset of normal cells (*53*).

As the clinical applications of ACT expand, it will be important to identify biomarkers that predict success. Analysis of tumor biopsies before therapy might identify signatures that predict susceptibility to ACT or define interventions that may be necessary to improve therapeutic efficacy. The ability of T cells to proliferate and/or persist in vivo has correlated with therapeutic efficacy after ACT for viral diseases and cancer. Thus, analysis of the functional properties of engineered T cells before transfer and their fate and function after transfer could provide insights into optimal compositions of ACT for therapeutic efficacy. Combining ACT with checkpoint-blocking antibodies, vaccines, and targeted drug therapies is supported by studies in animal models (*54*, *55*) and is beginning to be investigated in clinical trials.

The development of ACT, particularly with genetically modified T cells, has occurred predominantly in the United States. ACT with TILs for melanoma, CARs targeting CD19, TCRs for cancer, and gene-edited T cells for HIV have advanced to phase 2 clinical trials (NCT02228096, NCT01567891, NCT02348216, and NCT02225665), and it is likely that one or more of these T cell therapies will obtain eventual U.S. Food and Drug Administration (FDA) approval (Table 1). Regulatory agencies in Europe have not had the same experience in this field, and given the early success of this approach, these agencies are likely to be inundated with new applications and challenged by patient demand. The complexity of ACT makes it vital to educate patients and physicians regarding the appropriate indications and the particular toxicities and their management so as to avoid preventable adverse outcomes. New therapeutic technologies including ACT are expensive, and this will present additional challenges regarding reimbursement that are best overcome by clearly demonstrating therapeutic value and cost-effective outcome as compared with those of alternative therapies.

SUMMARY

Advances in genetic engineering have reinvigorated efforts to engineer T cells to be tumor-reactive to treat advanced human malignancies through adoptive transfer. Remarkable success in patients treated on trials at academic centers has enticed unprecedented interest from the biotechnology and pharmaceutical industry (Table 1), which is now rapidly advancing these approaches for FDA approval and accelerating research and development to safely apply ACT to a broad range of human diseases, from acute lymphoblastic leukemia (ALL) to glioblastoma to HIV. The field faces numerous scientific, regulatory, and economic obstacles and challenges in educating clinicians in the use of ACT. Surmounting these obstacles will require collaboration between academia and biotechnology in order to ensure that therapy with engineered T cells is established as a viable approach for common human malignancies. Results in cancer are likely to pave the way to ACT as a new approach for infections and autoimmunity.

REFERENCES AND NOTES

1. R. E. Billingham, L. Brent, P. B. Medawar, Quantitative studies on tissue transplantation immunity. II. The origin, strength and duration of actively and adoptively acquired immunity. *Proc. R. Soc. London Ser. B* **143**, 58–80 (1954).
2. L. Drujont, L. Carretero-Iglesia, L. Bouchet-Delbos, G. Beriou, E. Merieau, M. Hill, Y. Delneste, M. C. Cuturi, C. Louvet, Evaluation of the therapeutic potential of bone marrow-derived myeloid suppressor cell (MDSC) adoptive transfer in mouse models of autoimmunity and allograft rejection. *PLOS ONE* **9**, e100013 (2014).
3. S. Sattler, G.-S. Ling, D. Xu, L. Hussaarts, A. Romaine, H. Zhao, L. Fossati-Jimack, T. Malik, H. T. Cook, M. Botto, Y. L. Lau, H. H. Smits, F. Y. Liew, F. P. Huang, IL-10-producing regulatory B cells induced by IL-33 (Breg(IL-33)) effectively attenuate mucosal inflammatory responses in the gut. *J. Autoimmun.* **50**, 107–122 (2014).
4. S. R. Riddell, M. Elliott, D. A. Lewinsohn, M. J. Gilbert, L. Wilson, S. A. Manley, S. D. Lupton, R. W. Overell, T. C. Reynolds, L. Corey, P. D. Greenberg, T-cell mediated rejection of gene-modified HIV-specific cytotoxic T lymphocytes in HIV-infected patients. *Nat. Med.* **2**, 216–223 (1996).
5. J. Scholler, T. Brady, G. Binder-Scholl, W.-T. Hwang, G. Plesa, K. Hege, A. Vogel, M. Kalos, J. Riley, S. Deeks, R. Mitsuyasu, W. Bernstein, N. Aronson, B. Levine, F. Bushman, C. June, Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. *Sci. Transl. Med.* **4**, 132Ra153 (2012).
6. Y. C. Ho, L. Shan, N. N. Hosmane, J. Wang, S. B. Laskey, D. I. Rosenbloom, J. Lai, J. N. Blankson, J. D. Siliciano, R. F. Siliciano, Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. *Cell* **155**, 540–551 (2013).
7. G. Hütter, D. Nowak, M. Mossner, S. Ganepola, A. Müssig, K. Allers, T. Schneider, J. Hofmann, C. Kücherer, O. Blau, I. W. Blau, W. K. Hofmann, E. Thiel, Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.* **360**, 692–698 (2009).
8. J. J. Rossi, C. H. June, D. B. Kohn, Genetic therapies against HIV. *Nat. Biotechnol.* **25**, 1444–1454 (2007).
9. K. Deng, M. Pertea, A. Rongvaux, L. Wang, C. M. Durand, G. Ghiaur, J. Lai, H. L. McHugh, H. Hao, H. Zhang, J. B. Margolick, C. Gurer, A. J. Murphy, D. M. Valenzuela, G. D. Yancopoulos, S. G. Deeks, T. Strowig, P. Kumar, J. D. Sili-

ciano, S. L. Salzberg, R. A. Flavell, L. Shan, R. F. Siliciano, Broad CTL response is required to clear latent HIV-1 due to dominance of escape mutations. *Nature* **517**, 381–385 (2015).
10. A. M. Lesokhin, M. R. Callahan, M. A. Postow, J. D. Wolchok, On being less tolerant: Enhanced cancer immunosurveillance enabled by targeting checkpoints and agonists of T cell activation. *Sci. Transl. Med.* **7**, 280sr1 (2015).
11. N. van Rooij, M. M. van Buuren, D. Philips, A. Velds, M. Toebes, B. Heemskerk, L. J. van Dijk, S. Behjati, H. Hilkmann, D. El Atmioui, M. Nieuwland, M. R. Stratton, R. M. Kerkhoven, C. Kesmir, J. B. Haanen, P. Kvistborg, T. N. Schumacher, Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. *J. Clin. Oncol.* **31**, e439–e442 (2013).
12. M. M. Gubin, X. Zhang, H. Schuster, E. Caron, J. P. Ward, T. Noguchi, Y. Ivanova, J. Hundal, C. D. Arthur, W. J. Krebber, G. E. Mulder, M. Toebes, M. D. Vesely, S. S. Lam, A. J. Korman, J. P. Allison, G. J. Freeman, A. H. Sharpe, E. L. Pearce, T. N. Schumacher, R. Aebersold, H. G. Rammensee, C. J. Melief, E. R. Mardis, W. E. Gillanders, M. N. Artyomov, R. D. Schreiber, Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature* **515**, 577–581 (2014).
13. D. S. Chen, I. Mellman, Oncology meets immunology: The cancer-immunity cycle. *Immunity* **39**, 1–10 (2013).
14. C. H. Lamers, R. Willemsen, P. van Elzakker, S. van Steenbergen-Langeveld, M. Broertjes, J. Oosterwijk-Wakka, E. Oosterwijk, S. Sleijfer, R. Debets, J. W. Gratama, Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. *Blood* **117**, 72–82 (2011).
15. M. H. Kershaw, J. A. Westwood, L. L. Parker, G. Wang, Z. Eshhar, S. A. Mavroukakis, D. E. White, J. R. Wunderlich, S. Canevari, L. Rogers-Freezer, C. C. Chen, J. C. Yang, S. A. Rosenberg, P. Hwu, A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. *Clin. Cancer Res.* **12**, 6106–6115 (2006).
16. J. L. Davis, M. R. Theoret, Z. Zheng, C. H. Lamers, S. A. Rosenberg, R. A. Morgan, Development of human anti-murine T-cell receptor antibodies in both responding and nonresponding patients enrolled in TCR gene therapy trials. *Clin. Cancer Res.* **16**, 5852–5861 (2010).
17. L. P. Li, J. C. Lampert, X. Chen, C. Leitao, J. Popović, W. Müller, T. Blankenstein, Transgenic mice with a diverse human T cell antigen receptor repertoire. *Nat. Med.* **16**, 1029–1034 (2010).
18. M. R. Parkhurst, J. C. Yang, R. C. Langan, M. E. Dudley, D. A. Nathan, S. A. Feldman, J. L. Davis, R. A. Morgan, M. J. Merino, R. M. Sherry, M. S. Hughes, U. S. Kammula, G. Q. Phan, R. M. Lim, S. A. Wank, N. P. Restifo, P. F. Robbins, C. M. Laurencot, S. A. Rosenberg, T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. *Mol. Ther.* **19**, 620–626 (2011).
19. J. Corrigan-Curay, H. P. Kiem, D. Baltimore, M. O'Reilly, R. J. Brentjens, L. Cooper, S. Forman, S. Gottschalk, P. Greenberg, R. Junghans, H. Heslop, M. Jensen, C. Mackall, C. June, O. Press, D. Powell, A. Ribas, S. Rosenberg, M. Sadelain, B. Till, A. P. Patterson, R. C. Jambou, E. Rosenthal, L. Gargiulo, M. Montgomery, D. B. Kohn, T-cell immunotherapy: Looking forward. *Mol. Ther.* **22**, 1564–1574 (2014).
20. B. J. Cameron, A. B. Gerry, J. Dukes, J. V. Harper, V. Kannan, F. C. Bianchi, F. Grand, J. E. Brewer, M. Gupta, G. Plesa, G. Bossi, A. Vuidepot, A. S. Powlesland, A. Legg, K. J. Adams, A. D. Bennett, N. J. Pumphrey, D. D. Williams, G. Binder-Scholl, I. Kulikovskaya, B. L. Levine, J. L. Riley, A. Varela-Rohena, E. A. Stadtmauer, A. P. Rapoport, G. P. Linette, C. H. June, N. J. Hassan, M. Kalos, B. K. Jakobsen, Identification of a Titin-derived HLA-A1-presented peptide as a cross-reactive target for engineered MAGE A3-directed T cells. *Sci. Transl. Med.* **5**, 197ra103 (2013).
21. M. E. Birnbaum, J. L. Mendoza, D. K. Sethi, S. Dong, J. Glanville, J. Dobbins, E. Ozkan, M. M. Davis, K. W. Wucherpfennig, K. C. Garcia, Deconstructing the peptide-MHC specificity of T cell recognition. *Cell* **157**, 1073–1087 (2014).
22. C. J. Voskens, S. M. Goldinger, C. Loquai, C. Robert, K. C. Kaehler, C. Berking, T. Bergmann, C. L. Bockmeyer, T. Eigentler, M. Fluck, C. Garbe, R. Gutzmer, S. Grabbe, A. Hauschild, R. Hein, G. Hundorfean, A. Justich, U. Keller, C. Klein, C. Mateus, P. Mohr, S. Paetzold, I. Satzger, D. Schadendorf, M. Schlaeppi, G. Schuler, B. Schuler-Thurner, U. Trefzer, J. Ulrich, J. Vaubel, R. von Moos, P. Weder, T. Wilhelm, D. Göppner, R. Dummer, L. M. Heinzerling, The price of tumor control: An analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLOS ONE* **8**, e53745 (2013).
23. J. D. Wolchok, H. Kluger, M. K. Callahan, M. A. Postow, N. A. Rizvi, A. M. Lesokhin, N. H. Segal, C. E. Ariyan, R. A. Gordon, K. Reed, M. M. Burke, A. Caldwell, S. A. Kronenberg, B. U. Agunwamba, X. Zhang, I. Lowy, H. D. Inzunza, W. Feely, C. E. Horak, Q. Hong, A. J. Korman, J. M. Wigginton, A. Gupta, M. Sznol, Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* **369**, 122–133 (2013).
24. A. Mirsoian, M. N. Bouchlaka, G. D. Sckisel, M. Chen, C. C. Pai, E. Maverakis, R. G. Spencer, K. W. Fishbein, S. Siddiqui, A. M. Monjazeb, B. Martin, S. Maudsley, C. Hesdorffer, L. Ferrucci, D. L. Longo, B. R. Blazar, R. H. Wiltrout, D. D. Taub, W. J. Murphy, Adiposity induces lethal cytokine storm after systemic administration of stimulatory immunotherapy regimens in aged mice. *J. Exp. Med.* **211**, 2373–2383 (2014).
25. P. A. McSweeney, D. Niederwieser, J. A. Shizuru, B. M. Sandmaier, A. J. Molina, D. G. Maloney, T. R. Chauncey, T. A. Gooley, U. Hegenbart, R. A. Nash, J. Radich, J. L. Wagner, S. Minor, F. R. Appelbaum, W. I. Bensinger, E. Bryant, M. E. Flowers, G. E. Georges, F. C. Grumet, H. P. Kiem, B. Torok-Storb, C. Yu, K. G. Blume, R. F. Storb, Hematopoietic cell transplantation in older patients with hematologic malignancies: Replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* **97**, 3390–3400 (2001).
26. J. M. Kaldor, N. E. Day, F. Pettersson, E. A. Clarke, D. Pedersen, W. Mehnert, J. Bell, H. Høst, P. Prior, S. Karjalainen, F. Neal, M. Koch, P. Band, W. Choi, V. P. Kirn, A. Arslan, B. Zarén, A. R. Belch, H. Storm, B. Kittelmann, P. Fraser, M. Stovall, Leukemia following chemotherapy for ovarian cancer. *N. Engl. J. Med.* **322**, 1–6 (1990).
27. J. Hataye, J. J. Moon, A. Khoruts, C. Reilly, M. K. Jenkins, Naive and memory CD4+ T cell survival controlled by clonal abundance. *Science* **312**, 114–116 (2006).
28. J. A. Doudna, E. Charpentier, Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science* **346**, 1258096 (2014).
29. H. Kim, J. S. Kim, A guide to genome engineering with programmable nucleases. *Nat. Rev. Genet.* **15**, 321–334 (2014).
30. E. Provasi, P. Genovese, A. Lombardo, Z. Magnani, P. Q. Liu, A. Reik, V. Chu, D. E. Paschon, L. Zhang, J. Kuball, B. Camisa, A. Bondanza, G. Casorati, M. Ponzoni, F. Ciceri, C. Bordignon, P. D. Greenberg, M. C. Holmes, P. D. Gregory, L. Naldini, C. Bonini, Editing T cell specificity towards leukemia by zinc finger nucleases and lentiviral gene transfer. *Nat. Med.* **18**, 807–815 (2012).
31. B. Berdien, U. Mock, D. Atanackovic, B. Fehse, TALEN-mediated editing of endogenous T-cell receptors facilitates efficient reprogramming of T lymphocytes by lentiviral gene transfer. *Gene Ther.* **21**, 539–548 (2014).
32. P. Tebas, D. Stein, W. W. Tang, I. Frank, S. Q. Wang, G. Lee, S. K. Spratt, R. T. Surosky, M. A. Giedlin, G. Nichol, M. C. Holmes, P. D. Gregory, D. G. Ando, M. Kalos, R. G. Collman, G. Binder-Scholl, G. Plesa, W. T. Hwang, B. L. Levine, C. H. June, Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *N. Engl. J. Med.* **370**, 901–910 (2014).
33. H. Torikai, A. Reik, P. Q. Liu, Y. Zhou, L. Zhang, S. Maiti, H. Huls, J. C. Miller, P. Kebriaei, B. Rabinovitch, D. A. Lee, R. E. Champlin, C. Bonini, L. Naldini, E. J. Rebar, P. D. Gregory, M. C. Holmes, L. J. Cooper, A foundation for universal T-cell based immunotherapy: T cells engineered to express a CD19-specific chimeric-antigen-receptor and eliminate expression of endogenous TCR. *Blood* **119**, 5697–5705 (2012).
34. F. S. Hodi, S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J. I. Clark, J. D. Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos, W. J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* **363**, 711–723 (2010).
35. S. L. Topalian, F. S. Hodi, J. R. Brahmer, S. N. Gettinger, D. C. Smith, D. F. McDermott, J. D. Powderly, R. D. Carvajal, J. A. Sosman, M. B. Atkins, P. D. Leming, D. R. Spigel, S. J. Antonia, L. Horn, C. G. Drake, D. M. Pardoll, L. Chen, W. H. Sharfman, R. A. Anders, J. M. Taube, T. L. McMiller, H. Xu, A. J. Korman, M. Jure-Kunkel, S. Agrawal, D. McDonald, G. D. Kollia, A. Gupta, J. M. Wigginton, M. Sznol, Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* **366**, 2443–2454 (2012).
36. J. R. Brahmer, S. S. Tykodi, L. Q. Chow, W. J. Hwu, S. L. Topalian, P. Hwu, C. G. Drake, L. H. Camacho, J. Kauh, K. Odunsi, H. C. Pitot, O. Hamid, S. Bhatia, R. Martins, K. Eaton, S. Chen, T. M. Salay, S. Alaparthy, J. F. Grosso, A. J. Korman, S. M. Parker, S. Agrawal, S. M. Goldberg, D. M. Pardoll, A. Gupta, J. M. Wigginton, Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med.* **366**, 2455–2465 (2012).
37. P. Zhou, D. R. Shaffer, D. A. Alvarez Arias, Y. Nakazaki, W. Pos, A. J. Torres, V. Cremasco, S. K. Dougan, G. S. Cowley, K. Elpek, J. Brogdon, J. Lamb, S. J. Turley, H. L. Ploegh, D. E. Root, J. C. Love, G. Dranoff, N. Hacohen, H. Cantor, K. W. Wucherpfennig, In vivo discovery of immunotherapy targets in the tumour microenvironment. *Nature* **506**, 52–57 (2014).
38. A. Di Stasi, B. De Angelis, C. M. Rooney, L. Zhang, A. Mahendravada, A. E. Foster, H. E. Heslop, M. K. Brenner, G. Dotti, B. Savoldo, T lymphocytes coexpressing CCR4 and a chimeric antigen receptor targeting CD30 have improved homing and antitumor activity in a Hodgkin tumor model. *Blood* **113**, 6392–6402 (2009).
39. G. M. Bendle, C. Linnemann, L. Bies, J. Y. Song, T. N. Schumacher, Blockade of TGF-β signaling greatly enhances the efficacy of TCR gene therapy of cancer. *J. Immunol.* **191**, 3232–3239 (2013).
40. S. P. Kerkar, R. S. Goldszmid, P. Muranski, D. Chinnasamy, Z. Yu, R. N. Reger, A. J. Leonardi, R. A. Morgan, E. Wang, F. M. Marincola, G. Trinchieri, S. A. Rosenberg, N. P. Restifo, IL-12 triggers a programmatic change in dysfunctional myeloid-derived cells within mouse tumors. *J. Clin. Invest.* **121**, 4746–4757 (2011).
41. X. Wang, W. C. Chang, C. W. Wong, D. Colcher, M. Sherman, J. R. Ostberg, S. J. Forman, S. R. Riddell, M. C. Jensen, A transgene-encoded cell surface polypeptide for selection, in vivo tracking, and ablation of engineered cells. *Blood* **118**, 1255–1263 (2011).
42. B. Philip, E. Kokalaki, L. Mekkaoui, S. Thomas, K. Straathof, B. Flutter, V. Marin, T. Marafioti, R. Chakraverty, D. Linch, S. A. Quezada, K. S. Peggs, M. Pule, A highly compact epitope-based marker/suicide gene for easier and safer T-cell therapy. *Blood* **124**, 1277–1287 (2014).
43. C. Berger, M. E. Flowers, E. H. Warren, S. R. Riddell, Analysis of transgene-specific immune responses that limit

the in vivo persistence of adoptively transferred HSV-TK-modified donor T cells after allogeneic hematopoietic cell transplantation. *Blood* **107**, 2294–2302 (2006).
44. A. Di Stasi, S. K. Tey, G. Dotti, Y. Fujita, A. Kennedy-Nasser, C. Martinez, K. Straathof, E. Liu, A. G. Durett, B. Grilley, H. Liu, C. R. Cruz, B. Savoldo, A. P. Gee, J. Schindler, R. A. Krance, H. E. Heslop, D. M. Spencer, C. M. Rooney, M. K. Brenner, Inducible apoptosis as a safety switch for adoptive cell therapy. *N. Engl. J. Med.* **365**, 1673–1683 (2011).
45. G. M. Bendle, C. Linnemann, A. I. Hooijkaas, L. Bies, M. A. de Witte, A. Jorritsma, A. D. Kaiser, N. Pouw, R. Debets, E. Kieback, W. Uckert, J. Y. Song, J. B. Haanen, T. N. Schumacher, Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. *Nat. Med.* **16**, 565–570, 1p, 570 (2010).
46. H. Torikai, A. Reik, F. Soldner, E. H. Warren, C. Yuen, Y. Zhou, D. L. Crossland, H. Huls, N. Littman, Z. Zhang, S. S. Tykodi, P. Kebriaei, D. A. Lee, J. C. Miller, E. J. Rebar, M. C. Holmes, R. Jaenisch, R. E. Champlin, P. D. Gregory, L. J. Cooper, Toward eliminating HLA class I expression to generate universal cells from allogeneic donors. *Blood* **122**, 1341–1349 (2013).
47. C. Linnemann, M. M. van Buuren, L. Bies, E. M. Verdegaal, R. Schotte, J. J. Calis, S. Behjati, A. Velds, H. Hilkmann, D. E. Atmioui, M. Visser, M. R. Stratton, J. B. Haanen, H. Spits, S. H. van der Burg, T. N. Schumacher, High-throughput epitope discovery reveals frequent recognition of neo-antigens by CD4$^+$ T cells in human melanoma. *Nat. Med.* **21**, 81–85 (2015).
48. P. F. Robbins, Y. C. Lu, M. El-Gamil, Y. F. Li, C. Gross, J. Gartner, J. C. Lin, J. K. Teer, P. Cliften, E. Tycksen, Y. Samuels, S. A. Rosenberg, Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. *Nat. Med.* **19**, 747–752 (2013).
49. N. P. Restifo, L. Gattinoni, Lineage relationship of effector and memory T cells. *Curr. Opin. Immunol.* **25**, 556–563 (2013).
50. C. Gerlach, J. C. Rohr, L. Perié, N. van Rooij, J. W. van Heijst, A. Velds, J. Urbanus, S. H. Naik, H. Jacobs, J. B. Beltman, R. J. de Boer, T. N. Schumacher, Heterogeneous differentiation patterns of individual CD8$^+$ T cells. *Science* **340**, 635–639 (2013).
51. V. R. Buchholz, M. Flossdorf, I. Hensel, L. Kretschmer, B. Weissbrich, P. Gräf, A. Verschoor, M. Schiemann, T. Höfer, D. H. Busch, Disparate individual fates compose robust CD8$^+$ T cell immunity. *Science* **340**, 630–635 (2013).
52. C. Berger, D. Sommermeyer, M. Hudecek, M. Berger, A. Balakrishnan, P. J. Paszkiewicz, P. L. Kosasih, C. Rader, S. R. Riddell, Safety of targeting ROR1 in primates with chimeric antigen receptor-modified T cells. *Cancer Immunol. Res.* **2**, 206–216 (2015).
53. C. C. Kloss, M. Condomines, M. Cartellieri, M. Bachmann, M. Sadelain, Combinatorial antigen recognition with balanced signaling promotes selective tumor eradication by engineered T cells. *Nat. Biotechnol.* **31**, 71–75 (2013).
54. W. Peng, G. Lizée, P. Hwu, Blockade of the PD-1 pathway enhances the efficacy of adoptive cell therapy against cancer. *OncoImmunology* **2**, e22691 (2013).
55. R. C. Koya, S. Mok, N. Otte, K. J. Blacketor, B. Comin-Anduix, P. C. Tumeh, A. Minasyan, N. A. Graham, T. G. Graeber, T. Chodon, A. Ribas, BRAF inhibitor vemurafenib improves the antitumor activity of adoptive cell immunotherapy. *Cancer Res.* **72**, 3928–3937 (2012).

Funding: Research in the C.H.J., S.R.R., and T.N.S. laboratories is supported by grants 5R01CA165206, 5R01CA120409, 5R01CA114536, and 2R01CA136551; EU FP7 grants ATECT and SUPERSIST; and the K. G. Jebsen Center for Cancer Immunotherapy grant (to T.N.S.). **Competing interests:** C.H.J. has a sponsored research grant by, has licensed technology to, and consults for Novartis. T.N.S. holds equity stake in TCF and is on the advisory board of Cellectis (SAB). S.R.R. holds equity stake in, and is a cofounder of, Juno Therapeutics and is on the advisory board for and consults for Cell Medica.

10.1126/scitranslmed.aaa3643

Citation: C. H. June, S. R. Riddell, T. N. Schumacher, Adoptive cellular therapy: A race to the finish line. *Sci. Transl. Med.* **7**, 280ps7 (2015).