Comment

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Unlocking the potential of engineered immune cell therapy for solid tumors

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Adoptive cell therapy has emerged as a promising approach for treating advanced solid malignancies. Genetic engineering techniques represent an exciting area of research for the development of cellular products with enhanced cytotoxicity, phenotype, and metabolism.

The expanding role of cell therapy in solid tumors

Adoptive cell therapy (ACT) encompasses various strategies for the ex vivo manipulation of immune cells, including chimeric antigen receptor (CAR)-T cells, T-cell receptor (TCR)-transduced T cells, and tumor-infiltrating lymphocytes (TILs).

The transfer of unselected TILs has demonstrated potential for durable responses in advanced melanoma[1], even in patients refractory to anti-PD1 therapy[2], and the autologous TIL product lifileucel has become the first FDA-approved ACT for a solid tumor (Table 1). TIL therapy has also shown promising activity against other immunogenic malignancies, including non-small cell lung cancer[3] and cervical cancer[4]. Candidates for TIL therapy undergo resection of a tumor lesion, from which T cells are isolated, expanded and reinfused after lymphodepletion, usually followed by systemic interleukin-2 (IL2) administration to promote T cell survival and expansion in vivo. TILs possess the ability to traffic back to the tumor site and target a wide range of neoantigens, which provides an advantage in advanced solid cancers, characterized by significant heterogeneity. However, conventional TIL therapy is restricted to basally immune-infiltrated tumors and faces challenges such as the potential expansion of non-reactive bystander T cells, an immunosuppressive tumor microenvironment (TME), and the exhausted phenotype of transferred cells. Advances in the selective expansion of tumor neoepitope-specific TILs[5] and the identification of distinct transcriptional signatures in circulating tumor-reactive T cells[6] represent promising steps toward the design of next-generation TIL therapies.

CAR-T and TCR-T therapies differ from TIL therapy in that they use T cells derived from peripheral blood, which are transduced with receptors designed to target prespecified epitopes. Besides, CAR-T cells contain a costimulatory domain to induce proliferation and cytotoxicity upon contact with the antigen. Unlike conventional TIL therapy, these strategies can be applied to 'colder' tumors if suitable targets -preferentially expressed on malignant cells- are identified. The promising results of certain products, along with the recent approval of afamicel -MAGE-A4-targeted TCR therapy- for synovial sarcoma, highlight significant progress in this field. However, substantial challenges persist for these therapies in the complex genomic landscape of solid tumors, including impaired tumor homing, on-target off-tumor toxicity, the restriction of CARs to membrane antigens, and the reliance of TCR-T cells on matched human leukocyte antigens (HLA). While combinatorial approaches and low-affinity CARs are being explored to address the scarcity of appropriate antigens, strategies such as dual bispecific CAR-T cells may help overcome target downregulation[7].

ACT offers unique opportunities for genetic modifications during the manufacturing process, potentially addressing some of these challenges (Fig. 1). A better understanding of predictive biomarkers related to TIL phenotype[8] and insights from gene-edited CAR-T products for hematologic malignancies are paving the way for T-cell genetic engineering beyond CAR/TCR transduction. The identification of prognostic immune signatures across different tumor subtypes[9], including some upregulated in persistent tumor-reactive TIL clonotypes[10], may provide insights into editable pathways to overcome T cell suppression within the TME.

Genetic silencing of immunosuppressive molecules

One approach to enhancing ACT involves knocking out immune checkpoints and inhibitory molecules using gene-editing techniques such as CRISPR-Cas9. Transcription factor TOX[11], programmed cell death protein (PD1)[12], and lymphocyte activation gene 3 (LAG3)[12] are key regulators of T cell exhaustion and tumor immune evasion. Along with other exhaustion markers, PD1 expression appears to identify tumor-reactive TILs repertoires[13], aligning with the concept that T cell exhaustion is triggered by recurrent antigen exposure. This implies that differentiated tumor-reactive T cells are prone to acquiring a dysfunctional state with limited persistence and self-renewal, both critical factors for durable clinical responses to ACT[14].

PD1-inactivated TIL therapy has demonstrated enhanced antitumor reactivity in animal models[15] and is currently being evaluated in clinical trials (NCT05361174). Similarly, knocking out cytotoxic T-lymphocyte associated protein 4 (CTLA-4) increases T cell activity by enhancing the secretion of interferon (IFN)-γ and tumor necrosis factor (TNF)-α[16]. Nonetheless, recent evidence suggests that the effects of eliminating PD1 expression in CAR-T cells could be context-dependent, uniquely leading to enhanced sensitivity of cells with low-affinity CARs and CD28/ICOS costimulatory domains[17]. On the other hand, genetic ablation of immune checkpoints seems to hinder the subsequent memory of CD8 + T cells in the setting of anti-viral responses[18]. Thus, whether their permanent knockout may enhance ACT antitumor efficacy remains controversial.

As our understanding of T cell dysfunction grows, additional targets are being explored for gene editing. Suppressors of cytokine signaling (SOCS) proteins[19], the PR domain zinc finger protein 1 (PRDM1)[20], the phosphatase PPTN2[21], the type-I interferon transcriptional regulator EGR2[22], and the RAS GTPase-activating protein

Table 1 | Summary of major cell therapies for solid tumors (approved by FDA or with positive results in a randomized clinical trial)

Cell product	Setting	Results	Evidence	Status
Autologous non-selected TILs (lifileucel)	Advanced melanoma refractory to anti-PD1 + /- BRAF/MEK inhibitors (median 3 prior lines)	ORR 31.4% (CR 5.2%); mPFS: 4.1 m; mOS: 13.9 m	Multicenter phase II non-randomized trial (*n*: 153)[57]	Approved by FDA (Feb 2024)
Autologous non-selected TILs (academic)	Advanced melanoma (11% in 1st line; 86% refractory to anti-PD1 therapy)	ORR 49% (CR 20%); mPFS: 7.2 m; mOS: 25.8 m	Multicenter phase III randomized trial (*n*: 168)[1]	Not approved
MAGE-A4-targeted TCR-T therapy (afamicel)	Unresectable or metastatic synovial sarcoma refractory to chemotherapy (HLA-A*02)	ORR 39%; mPFS: 3.8 m; mOS: 15.4 m	Multicenter phase II non-randomized trial (*n*: 44)[58]	Approved by FDA (Aug 2024)

ORR overall response rate, *CR* complete response, *PR* partial response, *mPFS* median progression-free survival, *mOS* median overall survival.

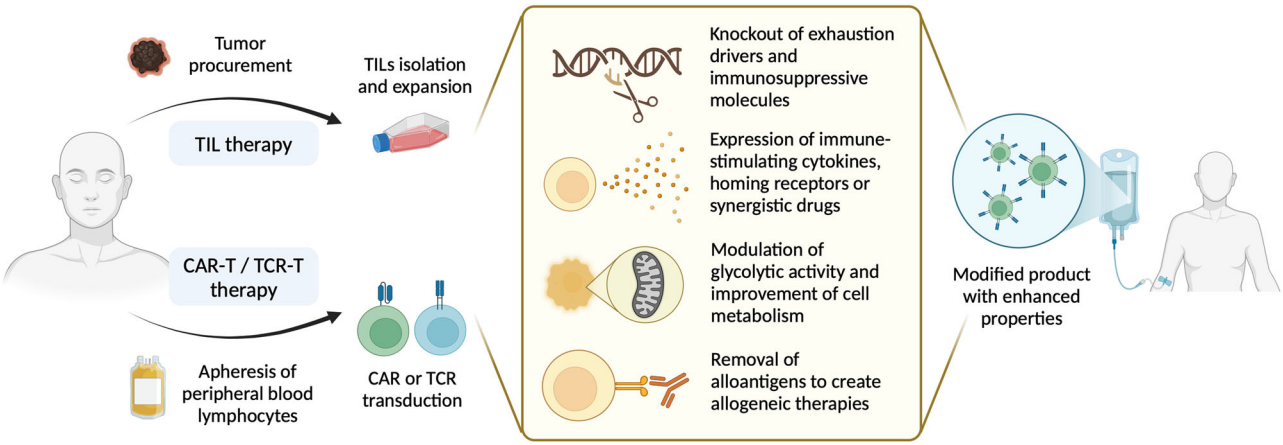

Fig. 1 | Overview of genetic engineering strategies and their applications in designing enhanced adoptive cell therapies. Created in BioRender. Yuste, A. (2025) https://BioRender.com/q80s946.

(RASA2)[23] are among the molecules involved in T cell exhaustion whose genetic knockout has been shown to improve antitumor activity. Forkhead box P3 (FOXP3), a key transcription factor associated with the regulatory T cell phenotype and overexpressed in cell products from non-responders[14], may also represent a compelling target. This approach could further extend to receptors of immunosuppressive signals, such as transforming growth factor-beta receptor 2 (TGFBR2)[24] and adenosine A2A receptor (A2AR)[25], as well as to post-transcriptional regulators of pro-inflammatory genes, including ribonuclease Regnase-1[26]. Genetic engineering could also be helpful to transiently silence CAR expression or reduce tonic CAR signaling in pre-exhausted CAR-T cells, thus restoring their functionality and leading to enhanced therapeutic activity[27].

'Armored' T cells: from stimulating cytokines to T cell engagers

Transferred T cells can be 'armed' with genes encoding pro-inflammatory molecules to boost their antitumor activity. IL12 overexpression in TILs was one of the first strategies aimed at enhancing T cell viability, although its use in patients with melanoma showed substantial toxicity with only transient clinical benefit[28], which prompted the search for new approaches. The inducible expression of IL18 in GD2-targeted CAR-T cells -triggered by GD2 antigen engagement- promotes cytokine release and antitumor activity in solid tumor xenografts[29]. Transduction of T cells with IL15, either alone[30] or in combination with membrane-tethered IL21[31], prevents CAR-T and TCR-T cell exhaustion and improves tumor regression in preclinical models. Notably, an engineered TIL product expressing membrane-bound IL15 has demonstrated encouraging results in advanced melanoma[32]. These interleukin-armed T cells could preserve their functionality in vivo without requiring systemic IL2. Together with de-escalating lymphodepleting chemotherapy, this strategy may reduce the toxicity of conventional TIL therapy and extend its use to more fragile patients.

Transducing TILs with chemotactic receptors -such as CXCR2[33]- facilitates T-cell trafficking to the TME and improves antitumor responses. In CAR-T cells, transduction of homing chemokines or receptors -including CXCL9[34], CXCR6[35], and co-expression of CCL19 with IL7[36]- has been shown to boost immune infiltration, cytokine secretion, and antitumor activity in pre-clinical models. Interestingly, engineering CAR-T cells to overexpress the transcription factor c-Jun diminishes terminal differentiation and renders them resistant to exhaustion[37]. Costimulatory T cell receptors, such as CD137 and CD27/CD28 -whose expression in transferred TILs has been correlated with clinical responses[14,38]- and potentially other pro-inflammatory markers may also serve as valuable candidates for genetic engineering.

Modified T cells capable of secreting bispecific T cell engagers (BiTEs) comprise another innovative strategy. CAR-T cells targeting epidermal growth factor receptor variant III (EGFR-vIII) transduced with anti-EGFR BiTEs are able to recruit untransduced bystander T lymphocytes, and their intra-ventricular infusion (CARv3-TEAM-T

therapy) resulted in transient but significant tumor regression in two out of three patients with recurrent glioblastoma[39]. Interestingly, autologous TILs transduced with BiTEs targeting CD3 and EGFR have shown tumor regression in lung cancer xenograft models[40]. These achievements are promising advances in the integration of BiTEs and other synergistic immunomodulatory agents into cellular therapies.

Genetic enhancement of T cell metabolism

The metabolic transformation required to meet the anabolic demands of malignant cells creates a hypoxic, acidic, and nutrient-deprived TME that significantly hampers immune cell survival. T cells engineered to express glycolytic enzymes or glucose transporters have demonstrated increased cytokine secretion, upregulation of activation markers, and enhanced antitumor activity in animal models[41]. Knocking out diacylglycerol (DAG)-kinase (DGK) increases intracellular DAG concentrations, which amplifies CD3/TCR signaling, thereby improving CAR-T cell effector functions and resistance to immunosuppressive factors[42]. Conditional deletion of monocarboxylate transporter 11 (MCT11) reduces lactic acid uptake and restores the functionality of exhausted T cells[43]. Overexpression of FOXO1[44] and transduction of IL10[45] have both been shown to enhance mitochondrial fitness and stem-like properties in CAR-T cells, increasing their antitumor activity in vivo. Similar results have been observed with EGFR-CAR-T cells engineered to express an inhibition-resistant PPAR-gamma coactivator 1α (PGC-1α)[46]. These findings highlight the potential of metabolic reprogramming in adoptively transferred T cells.

Inactivation of alloantigens: a pathway for more accessible products?

Beyond targeting immunosuppressive molecules, CRISPR-Cas9 technology can be leveraged to eliminate alloantigens from donor T cells for CAR/TCR transduction. Together with the use of gamma delta (γδ) CAR-T cells -whose TCRs recognize invariant antigens, independent from major histocompatibility complex (MHC) presentation-[47], alloantigen ablation may facilitate the development of universal cell products with minimal risk of immune rejection, addressing a critical limitation of allogeneic cell therapies. Knocking out HLA and endogenous TCR has proven feasible and could eventually allow the large-scale production of allogeneic T cell products, which can be stored and used off-the-shelf[48]. Transduction of a CD19-specific CAR into the TCR α constant (TRAC) locus results in increased T cell potency, uniform CAR expression, and reduced tonic CAR signaling, ultimately delaying terminal T cell differentiation[49]. The successful treatment of three patients with a TCR-T product targeting NY-ESO1, engineered through multiplex CRISPR-Cas9 to delete PD1 and TCR-α/β expression simultaneously, has demonstrated the safety and feasibility of multi-gene editing at a clinical scale, allowing the parallel inactivation of alloantigens alongside other genetic modifications[50].

Beyond T cells: engineered macrophage and NK cell therapies

As components of innate immunity, natural killer (NK) cells possess limited persistence and lack the capacity to generate memory phenotypes. However, unlike T cells, they do not rely on antigen presentation via the MHC, they can recognize stress-induced ligands, and target tumor cells that downregulate MHC to evade T cell interaction (a phenomenon known as 'missing self' recognition). This ability to detect a broader range of antigens and cancer cells, combined with their influence on TILs and other immune cells through cytokine secretion, has spurred interest in developing CAR-NK therapies for solid tumors, particularly those with dense stromal TMEs and advanced T-cell suppression mechanisms. Strategies to enhance CAR-NK cell potency and persistence -such as cytokine transduction, co-stimulatory signaling, and combined immune checkpoint blockade- represent an exciting area of research[51,52]. NK cells engineered to express CXCR2 exhibit improved tumor infiltration[53], and HLA knockout has proven feasible for developing allogeneic off-the-shelf NK therapies[54].

Given their strong effector functions and their ability to infiltrate tumors with an immune-suppressive TME, macrophages also represent valuable candidates for CAR transduction. CAR-macrophages have displayed pro-inflammatory properties and tumor regression in vitro[55]. Genetic modifications aimed at overcoming phagocytosis suppression, enhancing cytokine secretion, and promoting M1 polarization have emerged as promising strategies to optimize their antitumor effects[56].

Challenges for the clinical implementation of modified cell therapies

Genetic engineering introduces additional hurdles to the clinical implementation of ACT, including the need for advanced equipment, higher economic costs, and strict regulatory oversight for the authorization of genetically modified products. While centralized production at specialized institutions may favor regulatory compliance, this approach requires product cryopreservation for transportation and extensive inter-center coordination. Conversely, point-of-care manufacturing offers a compelling alternative by enabling the local production of advanced therapies, potentially lowering costs and increasing accessibility.

The potential for sustained clinical responses after a single administration not only offers clear clinical benefits and a positive impact on patients' quality of life but also carries a long-term cost-effectiveness advantage over chronic anti-cancer treatments. As mentioned above, genetic engineering may also aid in the design of allogeneic universal cell products. These could significantly reduce the costs, production times, and logistical complexities associated with personalized autologous therapies, thereby increasing their availability for centers without manufacturing capabilities.

Conclusions

Genetic engineering provides powerful tools to enhance the phenotype and functionality of adoptively transferred cells through diverse mechanisms. These include the knockout of immunosuppressive molecules, the overexpression of immune-stimulating interleukins, synergistic drugs or homing receptors, and the improvement of T cell metabolic fitness. Additionally, eliminating alloantigens paves the way for the development of more accessible allogeneic products. These advancements hold great promise for designing a new generation of cell therapies for the treatment of advanced solid tumors.

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Author contributions

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