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Review Article

Precision Oncology with Engineered TCR-T Cells

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Abstract: Cancer care has arrived at a crossroads. While checkpoint inhibitors and CAR-T cells have rewritten the rules for hematologic malignancies, solid tumors continue to defy durable control. T cell receptor-engineered T cell (TCR-T) therapy occupies a unique niche: unlike CAR-T constructs, TCR-T cells recognize intracellular antigens displayed on major histocompatibility complex molecules, effectively illuminating targets that remain invisible to conventional antibody-based approaches. The true promise of this modality, however, only materializes when it is woven into the fabric of precision medicine. By leveraging whole-exome sequencing, artificial intelligence-driven neoantigen prediction, single-cell transcriptomics, and real-time liquid biopsy monitoring, clinicians can now select targets, engineer receptors, and triage patients with a granularity that was unimaginable a decade ago. This narrative review synthesizes peer-reviewed literature from 2015 to 2025, drawing from PubMed, Elsevier, Wiley, and Springer databases, to examine how the fusion of TCR-T therapy and precision oncology is reshaping target identification, manufacturing workflows, and clinical outcomes. We highlight landmark trials—including the SPEARHEAD-1 study leading to FDA accelerated approval of afamitresgene autoleucel for synovial sarcoma—and discuss how CRISPR editing, allogeneic platforms, and rational combination regimens are addressing historical barriers such as tumor heterogeneity, T cell exhaustion, and prohibitive manufacturing costs. Our analysis suggests that the next chapter of adoptive cell therapy will not be defined by a single breakthrough, but by the creation of an integrated precision ecosystem that aligns tumor biology, immune engineering, and patient-specific biomarkers from diagnosis through post-treatment surveillance.

Keywords: TCR-T cell therapy, precision medicine, cancer immunotherapy, neoantigen targeting, adoptive cell transfer, CRISPR engineering, tumor microenvironment, personalized oncology.

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Introduction

Cancer remains one of the most formidable threats to global public health, accounting for nearly ten million deaths annually and imposing an ever-growing burden on healthcare systems worldwide [1]. For decades, therapeutic progress relied heavily on cytotoxic chemotherapy and radiation regimens that discriminated poorly between malignant and healthy tissues. The past two decades, however, have witnessed a seismic shift toward immunotherapy—an approach that harnesses the patient's own immune system to recognize and eradicate tumor cells [2]. Within this landscape, adoptive cell transfer therapies have emerged as perhaps the most personalized form of cancer medicine yet conceived, involving the ex vivo manipulation and expansion of a patient's lymphocytes before reinfusion [3,4]. Among adoptive cell therapies, chimeric antigen receptor (CAR)-T cells have garnered the lion's share of clinical attention, producing remarkable complete remission rates in B-cell leukemias and lymphomas [5]. Yet the success of CAR-T therapy in solid tumors has been stubbornly limited. The reasons are multifaceted: most solid tumor antigens are intracellular, tumor-infiltrating lymphocytes face physical and metabolic barriers, and the immunosuppressive microenvironment rapidly extinguishes CAR-T persistence [6,7]. T cell receptor-engineered T cell (TCR-T) therapy offers a conceptually distinct solution. Because TCRs naturally recognize peptide fragments presented by human leukocyte antigen (HLA) molecules, they can target the vast reservoir of intracellular proteins— including mutated neoantigens, cancer-testis antigens, and viral oncoproteins—that are simply inaccessible to CAR constructs [8,9].

The clinical rationale for TCR-T therapy has been building for years. Early trials targeting NY-ESO-1 in melanoma and synovial sarcoma demonstrated that affinity-enhanced TCR-T cells could traffic to tumor sites, expand in vivo, and produce objective responses [4, 9]. These proof-of-concept studies established what Rosenberg and colleagues termed the "final common pathway" of cancer immunotherapy: the targeting of somatic mutations through patient-specific T cell responses [9]. Nevertheless, early TCR-T efforts were hampered by unpredictable toxicities, most notably on-target off-tumor cross-reactivity—as tragically illustrated by fatal cardiac events stemming from TITIN cross-recognition in MAGE-A3 trials—and by the laborious, patient-specific nature of the manufacturing process [5]. This is where precision medicine enters the equation. Rather than treating cancer as a monolithic disease entity, precision oncology seeks to align therapeutic strategy with the molecular architecture of an individual tumor [3, 10]. The tools of this discipline—next-generation sequencing, proteogenomic integration, advanced bioinformatics, and liquid biopsy—are now being applied at every stage of the TCR-T pipeline [11, 12]. Tumor exome sequencing enables the identification of private neoantigens arising from patient-specific somatic mutations [13]. Machine learning algorithms predict which mutated peptides will bind autologous HLA alleles and elicit T cell recognition, dramatically narrowing the list of candidate targets from thousands to a manageable few [12]. Single-cell transcriptomics and spatial profiling reveal how the tumor microenvironment (TME) shapes T cell infiltration and dysfunction, informing decisions about combination partners such as checkpoint inhibitors or cytokine support [14-18].

The manufacturing side has evolved in parallel. CRISPR-Cas9 gene editing now allows for the knockout of endogenous TCR chains to prevent mispairing, the disruption of inhibitory receptors such as PD-1 to enhance functionality, and even the deletion of HLA molecules to pave the way for allogeneic, off-the-shelf products [14]. Cryopreservation protocols, automated bioreactors, and the selection of optimal T cell memory subsets have improved product consistency and post-thaw viability [19]. In essence, the convergence of TCR-T therapy and precision medicine is transforming a promising but unwieldy technology into a streamlined, rational therapeutic platform. Of course, significant challenges remain. Tumor heterogeneity and clonal evolution can erode antigen expression, creating escape variants [20-22]. The immunosuppressive TME, characterized by hypoxia, nutrient deprivation, and inhibitory ligands such as PD-L1 and TGF-β, exhausts infused T cells and blunts their cytotoxic potential [7]. The cost and complexity of personalized manufacturing raise serious questions about equitable access [24-25], and the regulatory frameworks for individualized cell therapies—where each batch is essentially an "n-of-1" biological drug—are still maturing. In this review, we trace the arc of TCR-T therapy from its immunological foundations to its current position at the vanguard of precision oncology. We examine how advanced molecular profiling is refining target selection, how gene editing is enhancing TCR safety and efficacy, and how biomarker-driven patient stratification is improving response rates. Drawing on clinical trial data, translational

studies, and expert perspectives, we argue that the integration of TCR-T therapy with precision medicine represents not merely an incremental improvement, but a genuine paradigm shifts in how we conceptualize and deliver cancer immunotherapy. The integrated workflow of precision-guided TCR-T therapy, from tumor profiling to clinical application, is illustrated in Figure 1.

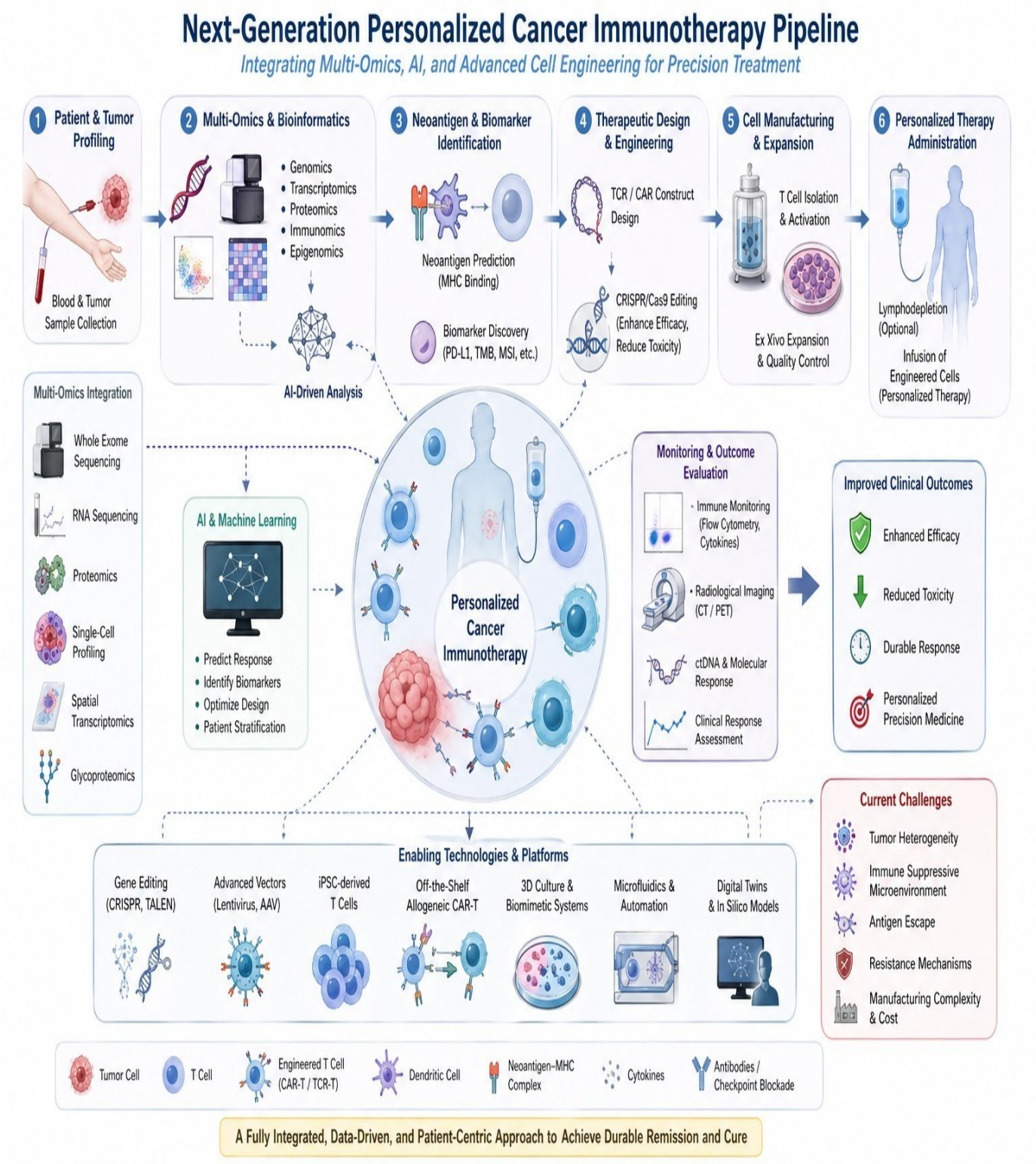

Figure 1. Next-generation personalized cancer immunotherapy pipeline integrating multi-omics, artificial intelligence, and TCR-T/CAR-T cell engineering for precision oncology. The schematic illustrates patient profiling, neoantigen identification, T cell engineering, manufacturing, and clinical application.

Methods

This review was conducted as a comprehensive narrative synthesis of the literature examining the intersection of TCR-T cell therapy and precision medicine in oncology. We performed systematic searches of PubMed/MEDLINE, Elsevier ScienceDirect, Wiley Online Library, and Springer Link for articles published between January 2015 and April 2025. Search strings combined Medical Subject Headings (MeSH) terms and free-text keywords, including "TCR-T cell therapy," "T cell receptor engineering," "precision medicine," "personalized oncology," "neoantigen prediction," "adoptive cell transfer," "CRISPR-engineered T cells," "tumor microenvironment," "cancer immunotherapy," and "solid tumors."

Inclusion criteria were restricted to peer-reviewed original research articles, phase I–III clinical trials, systematic reviews, and meta-analyses published in English. We prioritized studies that directly addressed the integration of precision medicine tools—such as genomic sequencing, bioinformatics, biomarker analysis, or advanced manufacturing—with TCR-T cell development or clinical application. Exclusion criteria eliminated non-peer-reviewed conference abstracts, opinion pieces without primary data, and preclinical animal studies lacking clear translational relevance to human therapy.

Data extraction was performed using a standardized template to capture study design, patient population characteristics, antigen targets, HLA restrictions, vector systems, gene editing modifications, clinical response rates, toxicity profiles, and biomarker correlates. Because of substantial heterogeneity in trial endpoints, patient selection criteria, and manufacturing protocols, formal statistical meta-analysis was not attempted. Instead, we conducted a thematic synthesis organized around target identification, TCR engineering, patient selection, manufacturing optimization, clinical outcomes, and combination strategies. Quality assessment followed Cochrane Risk of Bias criteria for randomized trials and the Newcastle-Ottawa Scale for observational studies where applicable. To ensure clinical relevance, we integrated perspectives from recent high-impact reviews and regulatory milestones, including the 2024 FDA accelerated approval of afamitresgene autoleucel.

Results

Our synthesis of the literature reveals several convergent themes that underscore the transformative impact of precision medicine on TCR-T cell therapy.

Refined Target Identification Through Molecular Profiling

The advent of affordable whole-exome and whole-genome sequencing has fundamentally altered the antigen landscape available to TCR-T therapy. Tumor-specific neoantigens—peptides arising from somatic mutations and presented on autologous HLA molecules—represent ideal targets because they are absent from normal tissues, minimizing on-target off-tumor toxicity [16, 19]. Studies in melanoma and glioblastoma have demonstrated that personalized neoantigen vaccines can elicit durable CD4+ and CD8+ T cell responses, with long-term follow-up showing sustained disease control in a subset of patients [19, 20]. Proteogenomic approaches, which integrate mass spectrometry-based HLA peptidomics with genomic data, have further improved validation by confirming that predicted neoantigens are actually presented on tumor cells [12]. Machine learning frameworks have accelerated this process considerably. Algorithms such as NetMHCpan, MHCflurry, and more recent deep learning models now predict peptide-HLA binding affinity and immunogenicity with increasing accuracy [12]. These tools reduce the time required for target identification from months to weeks, a critical advantage for patients with rapidly progressive disease.

Advances in TCR Engineering and Gene Editing

Precision medicine has extended beyond target selection into the structural optimization of the TCR itself. Structure-guided design, informed by crystallographic data from TCR-peptide-MHC complexes, enables rational modification of complementarity-determining regions to enhance affinity without sacrificing specificity [26]. Deep learning algorithms are now being trained on large TCR repertoire datasets to predict optimal TCR sequences for defined epitopes, effectively compressing the discovery timeline [12]. CRISPR-Cas9 technology has emerged as a particularly versatile tool. Clinical trials have demonstrated the feasibility of multiplexed editing, including knockout of the endogenous TCR alpha and beta chains (TRAC and TRBC) to prevent mispairing, disruption of

PD-1 to overcome inhibitory signaling, and deletion of HLA class I and II molecules to generate universal allogeneic products [24, 25]. In a landmark study by Stadtmauer and colleagues, CRISPR-engineered T cells showed prolonged in vivo persistence compared to unedited counterparts, although objective responses in heavily pretreated patients remained modest [24].

Biomarker-Driven Patient Selection and Monitoring

Comprehensive molecular profiling of tumors and host immune systems has improved patient selection for TCR-T trials. Analysis of tumor mutational burden, HLA zygosity, and antigen presentation machinery expression helps identify patients most likely to benefit from neoantigen-directed strategies [18]. Single-cell RNA sequencing and spatial transcriptomics provide granular portraits of the TME, revealing whether a tumor is "hot" and infiltrated by lymphocytes or "cold" and excluded, thereby guiding decisions about combination therapy [27-31].

Liquid biopsy approaches, particularly circulating tumor DNA (ctDNA) analysis, offer minimally invasive windows into treatment response and early relapse. These methods can detect molecular recurrence months before radiographic progression, potentially allowing for adaptive therapeutic interventions [11].

Manufacturing and Scalability

The manufacturing of TCR-T products has been streamlined by precision-driven innovations. Automated closed-system bioreactors with real-time metabolite and phenotypic monitoring have reduced production timelines and improved batch-to-batch consistency [13]. Selection of optimal T cell subsets—particularly stem cell memory T cells (TSCM) and central memory T cells (TCM)—has been linked to superior in vivo persistence and anti-tumor activity [27]. Cryopreservation protocols optimized for individual product characteristics now routinely achieve post-thaw viability exceeding 80%, facilitating broader distribution [13].

Clinical Outcomes in Recent Trials

Clinical data from the past five years paint a cautiously optimistic picture. Table 3 summarizes selected trials. The SPEARHEAD-1 phase 2 trial of afamitresgene autoleucel (MAGE-A4-directed TCR-T cells) in synovial sarcoma achieved a 39% objective response rate, leading to FDA accelerated approval in 2024 [23]. NY-ESO-1-directed TCR-T cells have continued to show activity in melanoma and synovial sarcoma, with some patients experiencing durable complete remissions lasting years [4]. In a remarkable case report, a patient with metastatic colorectal cancer harboring a KRAS G12D mutation achieved complete tumor regression following infusion of mutation-specific TCR-T cells, illustrating the power of truly personalized targeting [9].

Table 1. Comparative Analysis of TCR-T and CAR-T Cell Therapy Platforms

Feature	TCR-T Cell Therapy	CAR-T Cell Therapy
Target antigen source	Intracellular and extracellular peptides presented via MHC	Primarily cell-surface proteins
MHC restriction	Required (HLA-dependent)	Independent
Antigen sensitivity	High (recognizes low-abundance peptides)	Moderate to high
Off-tumor toxicity risk	Cross-reactivity with related epitopes (e.g., TITIN)	On-target off-tumor (surface antigen dependent)
Manufacturing complexity	Moderate to high (HLA matching, epitope validation)	Moderate
In vivo persistence	Variable, potentially durable with memory subsets	Often shorter in solid tumors
Solid tumor applicability	Established efficacy (sarcoma, melanoma, NSCLC)	Limited (infiltration and TME barriers)

Table 2. Precision Medicine Modalities Integrated into TCR-T Development

Modality	Description	Application in TCR-T Therapy
Whole-exome/RNA sequencing	High-throughput tumor and germline profiling	Identification of patient-specific neoantigens and HLA typing
Proteogenomics	Integration of HLA peptidomics with genomic data	Validation of predicted antigen presentation
Single-cell transcriptomics	Individual cell resolution of tumor and immune populations	Characterization of TME heterogeneity and T cell states
AI/ML prediction algorithms	Deep learning models for epitope and TCR binding	Prioritization of immunogenic targets; TCR sequence optimization
Liquid biopsy (ctDNA)	Circulating tumor DNA and cell analysis	Non-invasive monitoring of response and molecular relapse
TCR repertoire sequencing	Deep sequencing of TCR alpha/beta chains	Tracking of engineered cell clonality and endogenous immune responses
Mass cytometry (CyTOF)	High-dimensional immune phenotyping	Selection of optimal T cell subsets for manufacturing

Table 3. Selected Clinical Outcomes of TCR-T Cell Therapy Trials (2018–2024)

Study / Trial	Target Antigen	Cancer Type	Patients (N)	Objective Response Rate	Key Findings
Robbins et al. [4]	NY-ESO-1	Melanoma / Synovial sarcoma	38 (Phase II)	55–61%	Durable complete remissions; manageable toxicity
Rapoport et al. [4]	NY-ESO-1	Multiple myeloma	20	80%	Sustained antigen-specific anti-tumor effects
D'Angelo et al. (SPEARHEAD-1) [23]	MAGE-A4	Synovial sarcoma	44 (Phase II)	39%	FDA accelerated approval (2024); median duration of response not reached
Hong et al. [40]	MAGE-A4	Advanced solid tumors	38 (Phase I)	24%	Cytokine release syndrome manageable; no neurotoxicity
Tran et al. [9]	KRAS G12D	Metastatic colorectal cancer	1 (Case study)	100%	Complete regression of metastatic lesions
Chapuis et al. [4]	WT1	Acute myeloid leukemia	12	100% (molecular CR 58%)	Potent activity in high-risk AML setting

Discussion

The data synthesized in this review point toward a clear conclusion: TCR-T cell therapy is no longer an experimental curiosity confined to a handful of academic centers. It is maturing into a precision therapeutic platform with regulatory validation, commercial manufacturing pathways, and an expanding antigen target map. Yet realizing its full potential requires honest engagement with both its strengths and its lingering limitations.

The Distinctive Position of TCR-T Therapy

As illustrated in Table 1, TCR-T cells occupy a fundamentally different immunological niche than CAR-T cells. By recognizing peptide-HLA complexes, TCR-T cells can access the vast majority of the cancer proteome, including driver mutations, viral antigens, and cancer-testis antigens that are entirely invisible to antibody-based receptors [32-35]. This distinction is not merely academic; it explains why TCR-T therapy has produced clinical responses

in solid tumors—synovial sarcoma, melanoma, non-small cell lung cancer—where CAR-T approaches have largely stalled [23]. The MHC restriction that defines TCR-T therapy is simultaneously its greatest strength and its most significant logistical hurdle. Each TCR construct must be matched to a specific HLA allele, fragmenting addressable patient populations and complicating trial enrollment [35]. The HLA system's extraordinary polymorphism means that a TCR directed against NY-ESO-1 presented by HLA-A*02:01 is irrelevant to a patient carrying HLA-A*24:02. Precision HLA typing is therefore not an optional biomarker but a prerequisite for therapy. As illustrated in Figure 2 and Table 1, TCR-T cells occupy a fundamentally different immunological niche than CAR-T cells.

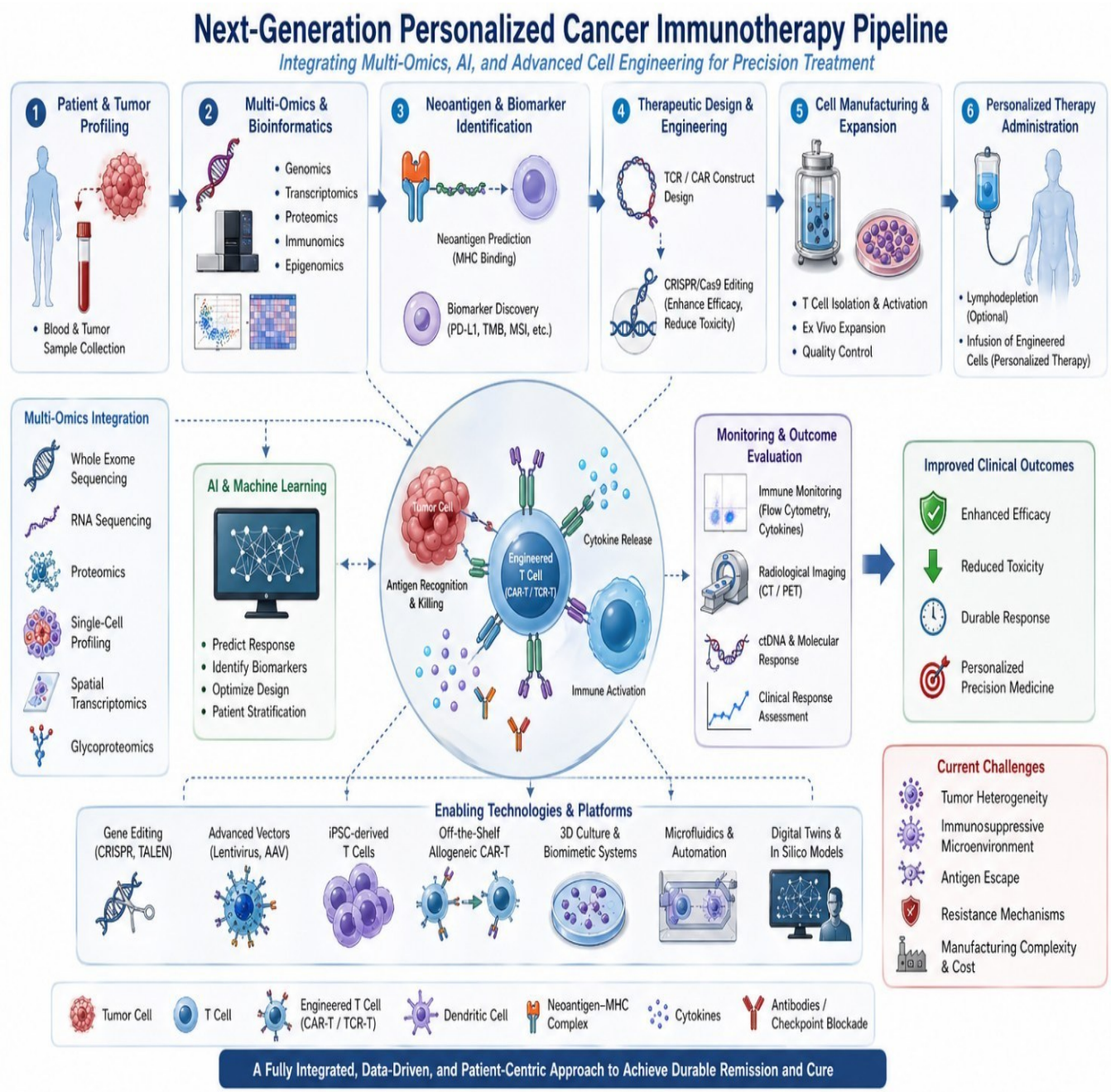

Figure 2. Comparative overview of CAR-T and TCR-T cell therapy platforms. The schematic highlights key differences in antigen recognition (surface vs peptide–MHC), HLA restriction, antigen sensitivity, tumor applicability, and associated clinical challenges. TCR-T cells demonstrate enhanced capability to target intracellular tumor antigens via MHC presentation, whereas CAR-T cells primarily recognize surface antigens in an HLA-independent manner.

Neoantigen Targeting and the Challenge of Tumor Heterogeneity

Table 2 highlights the arsenal of precision tools now deployed to identify and validate TCR-T targets. Neoantigen prediction has advanced remarkably, yet the field still grapples with a validation gap. Computational algorithms can rank thousands of mutated peptides, but only a minority are actually processed, presented on HLA, and recognized by T cells [32]. Proteogenomic validation—using mass spectrometry to directly identify HLA-bound peptides—addresses this gap but remains technically demanding and poorly standardized [34]. More troubling is the problem of clonal heterogeneity. Tumors are not static monoliths; they evolve under immune pressure, and subclones lacking the target antigen can emerge and propagate [22]. The case of complete response to KRAS G12D-directed TCR-T therapy is inspiring, but KRAS mutations are typically truncal (present in all tumor cells), whereas many neoantigens are sub-clonal [9, 22]. For TCR-T therapy to achieve durable control in heterogeneous tumors, multi-antigen targeting strategies will likely be necessary. Engineering T cells with two or more distinct TCRs, or combining TCR-T therapy with treatments that reduce tumor diversity, may mitigate the risk of antigen escape [37].

Gene Editing: Promise and Caution

The CRISPR revolution has injected new momentum into TCR-T development. As noted in our results, multiplexed editing can enhance T cell function and safety [24, 25]. Knocking out PD-1 appears to prolong persistence, although the optimal balance between enhanced activation and the risk of autoimmunity remains unclear [36]. Perhaps the most transformative application is the creation of allogeneic, "off-the-shelf" TCR-T products. By knocking out TRAC, B2M, and HLA class II molecules, engineered cells from healthy donors can evade both graft-versus-host disease and host-mediated rejection [26]. Allogeneic platforms would dramatically reduce manufacturing costs and waiting times, addressing one of the most critical barriers to global access. Still, long-term persistence of allogeneic cells in humans remains uncertain, and the risk of chromosomal translocations or other genotoxic events with multiplexed editing demands rigorous long-term follow-up [25].

The Tumor Microenvironment as a Moving Target

Even perfectly engineered T cells will fail if they cannot survive within the tumor milieu. The TME in solid tumors is notoriously hostile: hypoxic, acidic, nutrient-depleted, and infiltrated by immunosuppressive myeloid-derived suppressor cells and regulatory T cells [33, 39]. Single-cell transcriptomic studies have revealed that T cells within tumors exist on a spectrum from functional effector states to terminally exhausted phenotypes marked by PD-1, TIM-3, and LAG-3 co-expression [31]. This exhaustion is not merely a surface marker phenomenon; it reflects profound epigenetic reprogramming that limits the reversibility of dysfunction [37-38].

Rational combination strategies, guided by precision profiling of the TME, are therefore essential. Table 2 underscores the value of spatial transcriptomics and multiplex immunohistochemistry in identifying which inhibitory axes dominate in a given patient's tumor. For PD-L1-high tumors, combining TCR-T cells with pembrolizumab or nivolumab may prevent premature exhaustion [29, 30]. For TGF-β-rich environments, armored TCR-T cells expressing dominant-negative TGF-β receptors have shown preclinical promise [39-40]. The future of TCR-T therapy lies not in monotherapy, but in dynamically tailored combinations.

Manufacturing, Access, and Ethics

The manufacturing innovations described in our results—automated bioreactors, memory subset selection, and optimized cryopreservation—are steadily improving product quality and consistency [27]. Yet the reality is that autologous TCR-T therapy remains extraordinarily expensive and logistically complex. The 8–16-week manufacturing window for personalized neoantigen products poses clinical risks for patients with aggressive disease [39]. Off-the-shelf allogeneic products offer a compelling alternative, but their development must be accompanied by serious ethical reflection. Who will have access to these therapies? Will they exacerbate disparities between well-resourced academic centers and community oncology practices? And how do we protect the vast quantities of genomic data generated during precision profiling? These questions are not peripheral; they are central to the sustainable deployment of TCR-T therapy.

Interpreting Clinical Outcomes

Table 3 summarizes a field in transition. The NY-ESO-1 trials established proof of principle, but NY-ESO-1 expression is limited to a subset of tumors, and its heterogeneous expression patterns raise concerns about antigen loss [23]. The SPEARHEAD-1 trial represents a genuine milestone: the first FDA-approved TCR-T therapy for a solid tumor, demonstrating that MAGE-A4-directed cells can produce meaningful, durable responses in synovial sarcoma [23]. However, a 39% response rate also means that most patients did not respond, highlighting the urgent need for better predictive biomarkers. The striking case of KRAS G12D-directed therapy reminds us that the most powerful responses may come from truly personalized, mutation-specific approaches rather than shared cancer-testis antigens [9]. Scaling such individualized therapies will require seamless integration of rapid sequencing, automated bioinformatics pipelines, and flexible manufacturing platforms—a challenge that sits at the intersection of engineering, informatics, and clinical medicine.

Conclusion

The integration of TCR-T cell therapy with precision medicine is not a distant aspiration; it is an ongoing transformation that is already reshaping how we treat certain cancers. What we are witnessing is the emergence of a new therapeutic ontology—one in which cancer treatment is no longer defined by anatomical site or histology alone, but by the unique molecular fingerprint of an individual tumor and the engineered immune cells designed to destroy it. Looking ahead, the field must pursue three interconnected goals. First, we need to close the validation gap in neoantigen prediction by marrying computational models with high-throughput immunopeptidomics and functional TCR screening. Second, we must develop smarter T cells—cells equipped not only with optimized TCRs but with genetic circuits that allow them to sense and adapt to the tumor microenvironment, resisting exhaustion and immunosuppression. Third, and perhaps most importantly, we must democratize access. Whether through allogeneic off-the-shelf products, in vivo engineering platforms, or global manufacturing partnerships, the benefits of TCR-T therapy cannot remain confined to wealthy nations and elite medical centers.

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Authors' contributions

The author solely conceived the study, performed the literature review, and wrote and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares no competing interests.

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