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Application of Genomics in CAR T-Cell Therapy: A Comprehensive Review

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Abstract

Cancer is a genetically driven disease characterized by the progressive accumulation of somatic mutations, chromosomal aberrations, epigenetic dysregulation, and transcriptional reprogramming that collectively promote malignant transformation and immune escape. This genomic instability generates profound tumour heterogeneity, driving therapeutic resistance, immune evasion, and disease relapse. These challenges have accelerated the development of precision immunotherapies, such as chimeric antigen receptor (CAR) T-cell therapy, that leverage genetic engineering to overcome tumour complexity. CAR T cell therapy has emerged as a transformative approach for treating haematological malignancies. Cancer which is one of the comprehensive burdens responsible for approximately 20 million new cases and 10 million deaths globally each year, reqiures innovative treatments such as CAR T cell therapy are increasingly essential for managing refractory and difficult-to-treat cancers. The integration of genomics into CAR T cell research and clinical practice has substantially advanced target discovery, patient stratification, therapy optimization, and safety evaluation. Cutting-edge technologies including next-generation sequencing, single-cell genomics, transcriptomics, and Clustered Regularly Interspaced Short Palindromic Repeats screening have provided crucial insights into tumour heterogeneity, antigen expression, immune evasion, and CAR T cell functionality. This review summarizes the classification and mechanisms of CAR T cell therapies and highlights the diverse applications of genomics in their development and clinical implementation, alongside current limitations and future perspectives.

Keywords: CAR T cell Therapy; Genomics; Clustered Regularly Interspaced Short Palindromic Repeats; Next Generation Sequencing; Transcriptomics; Immunotherapy; Tumour Heterogeneity; Antigen Expression

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Abbreviations

Major Histocompatibility Complex (MHC), Chimeric antigen receptor (CAR), Next-generation sequencing (NGS), Fas ligand (FasL), Tumour microenvironment (TME), Artificial intelligence (AI), T cell Receptor Alpha Constant gene (TRAC), Human Leukocyte Antigen (HLA), Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/ CRISPR associate protein 9 (Cas9), T cells Redirected for Universal Cytokine Killing (TRUCKs), TNF (Tumour necrosis factor), IFN γ (interferon- γ), Tumour Necrosis Factor - α (TNF α), Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL), Granzyme B (GZMB), Protease inhibitor-9 (PI9), Granzyme A (GZMA), Ribonucleic Acid (RNA), Cluster of Differentiation 19/3/28 (CD19/3/28), B-cell Maturation Antigen (BCMA), G protein-coupled receptor, class C, group 5, member D (GPRC5D), Fc receptor-homolog 5 (FcRH5), C-type lectin-like molecule-1 (CLL-1), Cytokine release syndrome (CRS), Nuclear Receptor Subfamily 4A family of transcription factors (NR4A), Thymocyte selection-associated HMG-BOX (TOX), Polymerase Chain Reaction (PCR), T-Cell Factor 7 (TCF7), C-C Motif Chemokine Receptor 7 (CCR7), Granulocyte-Macrophage Colony-Stimulating Factor (GM CSF), Interleukin 6 (IL6), Interleukin 1β (IL-1β), Interferon-gamma (IFNG), Tumour Necrosis Factor (TNF), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), Cytokine Release Syndrome (CRS), Human Epidermal Growth Factor Receptor 2 (HER2), Molecular Imaging of CAR-T Cell Therapy or Imaging the CAR-T therapy in vivo (MAGE) and Programmed Cell Death Protein 1 (PD1)

Introduction

Chimeric Antigen Receptor (CAR) T cell therapy represents a paradigm shift in cancer immunotherapy by genetically engineering patient-derived T lymphocytes to recognize tumour-associated antigens independently of major histocompatibility complex (MHC) presentation [1]. This approach has shown remarkable efficacy in haematological malignancies. However, challenges persist in optimizing target design, enhancing T cell efficacy and persistence, and reducing therapy-related toxicities. Previous reviews have examined clinical trial advances, molecular mechanisms, and patient selection considerations for CAR T therapy [2]. Despite its success, particularly in B cell malignancies, therapeutic resistance, antigen loss, and adverse events remain significant hurdles [3].

Genomics has become indispensable in addressing these challenges, enabling comprehensive molecular characterization of both tumour and engineered T cells [3]. Integrative genomic approaches allow precise antigen selection, prediction of patient response, and design of next-generation CAR constructs [4]. Advances in gene-editing platforms, particularly Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/ CRISPR associate protein 9 (Cas9) and its derivatives, have opened new avenues for overcoming limitations in solid tumour treatment. By permitting multiplex genome editing, CRISPR enables simultaneous modification of multiple genes, enhancing CAR T cell efficacy, persistence, and safety [5]. This review emphasizes the role of gene-editing technologies in optimizing CAR T therapy and highlights the importance of genomics in guiding clinical application (Table 1).

General Mechanism of CAR T Cell Therapy

CAR T cell therapy has demonstrated significant success in hematologic malignancies, including leukaemia and lymphomas, often inducing prolonged remission [11, 12, 13]. However, therapy resistance and challenges in solid tumour treatment remain [14, 15]. Understanding T cell-mediated cytotoxicity is crucial for further progress. Studies using two-photon microscopy indicate that CAR T- cells kill tumour cells through repeated engagement, inducing apoptosis and detachment [16]. T cells utilize multiple cytotoxic mechanisms, including cytokine release, Tumour necrosis factor (TNF) family signalling, and exocytosis of cytotoxic enzymes [17, 18].

Cytokines such as interferon- γ (IFN γ) enhance tumour cell susceptibility to T cell killing by up regulating antigen and MHC class I presentation and stimulating Tumour Necrosis Factor - α (TNF α) production [19, 20, 21]. Fas ligand (FasL) expressed on T cells and TNF - Related Apoptosis-Inducing Ligand (TRAIL) on monocytes directly induce apoptosis through death-inducing signalling complexes [18, 21, 24]. Granzymes, particularly granzyme B (GZMB), enter target cells via perforin-mediated pores to trigger apoptosis [25, 26, 27, 28], with the inhibitor protease inhibitor-9 (PI9) acting as a potential mediator of tumour resistance [20]. Studies indicate that CAR T- cells utilize redundant cytotoxic pathways, as combined inhibition of granzyme A (GZMA), GZMB, and FasL significantly reduces cytotoxicity, highlighting the importance of multiple effector mechanisms (Figure 1).

The therapeutic process begins with leukapheresis to collect autologous T cells, followed by genetic modification using viral or non-viral vectors to introduce CAR constructs [23]. After ex vivo expansion, CAR T- cells are reinfused post lymphodepletion [24]. Upon antigen encounter, CAR T- cells activate, proliferate, and mediate cytotoxicity via perforin and granzymes [25]. Genomic and transcriptomic analyses reveal that CAR signalling activates complex transcriptional programs governing effector differentiation, memory formation, and exhaustion [26], while single-cell Ribonucleic Acid (RNA) sequencing identifies heterogeneity within CAR T populations, correlating specific gene signatures with clinical outcomes [27] (Figure 2).

Applications of Genomics in Car T Cell Therapy

Genomics Driven Target Identification and Validation

The initial and arguably most critical application of genomics in CAR T cell therapy lies in the identification and validation of appropriate tumour antigens. By leveraging large scale transcriptomic and genomic data sets, researchers can distinguish antigens that are highly expressed on cancer cells yet minimally present on normal tissue, greatly reducing the risk of off tumour toxicity [31, 32]. For example, CD19 and B-cell Maturation Antigen (BCMA) have been validated across multiple haematological malignancies through whole exome and RNA sequencing, establishing them as robust targets for CAR design [31, 32]. More recently, integrated genomic analyses have identified emerging targets such as G protein-coupled receptor, class C, group 5, member D (GPRC5D), Fc receptor-homolog 5 (FcRH5), and C-type lectin-like molecule-1 (CLL-1) that demonstrate restricted normal tissue expression and strong tumour enrichment, which enhances both safety and efficacy [32, 80, 81]. Single cell sequencing further refines this process by revealing intra tumour expression heterogeneity, ensuring that selected antigens are uniformly present across malignant subpopulations rather than limited to a subset of clones [53, 54]. This genomic precision in target discovery is foundational to effective CAR T therapy.

Table 1: Classification of CAR T-Cell Therapy.

CAR Generation	Structural Components	Functional Characteristics	Reference
First Generation	Antigen-binding domain + Cluster of Differentiation (CD) 3 chain	Provides primary T-cell activation only; limited expansion, survival, and therapeutic efficacy	[5, 6]
Second Generation	Antigen-binding domain + CD3 + one co-stimulatory domain (CD28 or 4-1BB)	Enhanced proliferation, persistence, and antitumor activity	[6, 7]
Third Generation	Antigen-binding domain + CD3 + two co-stimulatory domains	Increased cytokine production, cytotoxicity, and memory T-cell development; risk of overactivation	[7, 51]
Fourth Generation (TRUCKs)	Second-generation CARs with inducible cytokine expression (e.g., IL-12)	Modifies tumour microenvironment and recruits additional immune cells	[8, 67]
OptimizationStrategies	Genomic and transcriptomic profiling–guided CAR design	Improved safety, durability, and reduced T-cell exhaustion	[9, 25, 52]

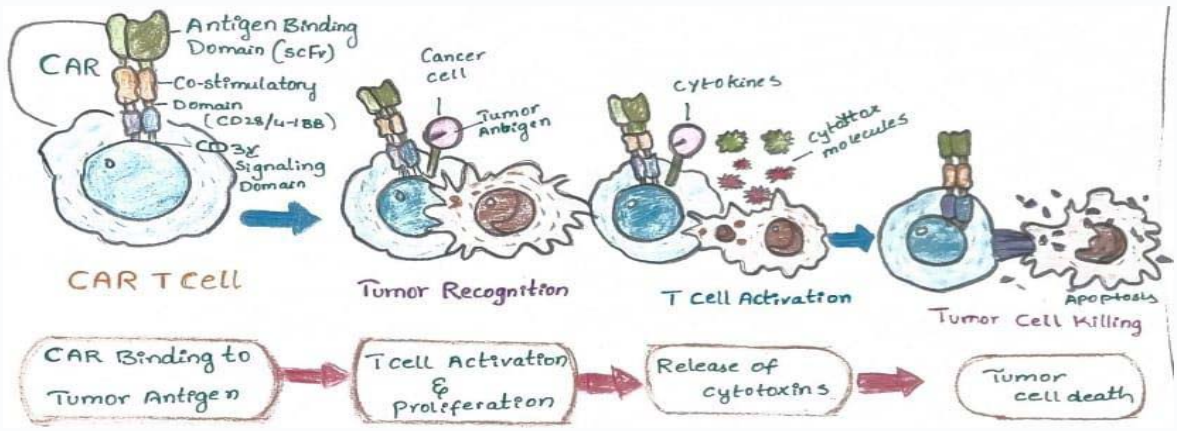

Figure 1: Mechanism of a CAR T- cell.

Genomics Informed Patient Selection and Risk Stratification

Genomic profiling of both tumour and host significantly improves patient selection by identifying molecular features predictive of response or adverse outcomes. Tumour genomics can reveal alterations in pathways such as antigen processing, interferon signalling, and apoptotic mechanisms that either facilitate or hinder CAR T cell recognition and killing [33, 34]. Patients with disruptions in antigen presentation machinery, for instance, often exhibit poor responses due to reduced neoantigen display on the tumour surface [34]. Similarly, germline and tumour variations in cytokine regulatory genes have been correlated with higher incidences of severe cytokine release syndrome (CRS) and neurotoxicity, allowing clinicians to anticipate and pre emptively manage these toxicities [35,40,66]. By integrating genomic risk scores with clinical parameters, providers can tailor pre conditioning regimens, adjust CAR T dosing, and implement close monitoring for high-risk patients, ultimately enhancing safety without sacrificing efficacy [33, 35].

Genomic Optimization of CAR Construct Architecture

Genomic technologies are transforming how CAR constructs are engineered to improve performance and durability. CRISPR based functional genomic screens have identified genes that regulate T cell exhaustion, metabolic fitness, and differentiation state, revealing actionable targets to enhance CAR T function [28, 61]. Notably, gene knockout of transcriptional regulators such as Nuclear Receptor Subfamily 4A family of transcription factors (NR4A) family members and Thymocyte selection-associated HMG-BOX (TOX) has been shown to reduce functional exhaustion, increasing persistence and antitumor activity in preclinical models [29, 62]. Additionally, genomic engineering to insert CAR constructs into precise genomic "safe harbors" like the T-cell receptor alpha constant gene (TRAC) locus ensures consistent CAR expression and reduces the risk of random insertional mutagenesis associated with viral vectors [61]. These genomics guided construct improvements translate into increased proliferation, reduced tonic signaling, and improved clinical outcomes in early trials [63, 59]. As new genomic insights emerge, CAR designs will continue to evolve toward greater specificity and sustained therapeutic potency.

Monitoring Therapeutic Response, Expansion, and Persistence

Post infusion monitoring of CAR T cell kinetics and tumour response is greatly enhanced by genomic assays that quantify CAR transgene presence and assess clonal dynamics. Techniques such as quantitative Polymerase Chain Reaction (PCR) and Next-Generation Sequencing (NGS) based vector tracking enable precise measurement of CAR T expansion, peak levels, and persistence over time, which correlate strongly with clinical remission or relapse [38, 41]. Patients maintaining detectable CAR T levels beyond 6–12 months typically demonstrate longer progression free survival compared with those with early contraction [69, 70]. Single cell RNA sequencing provides additional resolution by identifying functional subsets within CAR T populations, such as memory-like cells expressing T-Cell Factor 7 (TCF7) and C-C Motif Chemokine Receptor 7 (CCR7), which are associated with durable responses [27, 70]. Furthermore, integration site analysis confirms a diverse polyclonal expansion in responders, enhancing safety and mitigating concerns over oligoclonal dominance or insertional oncogenesis [41]. Collectively, these genomic monitoring approaches allow real time evaluation of treatment efficacy and early detection of resistance.

Prediction and Management of CAR T Associated Toxicities

Genomics has significantly advanced understanding of the biological drivers of CAR T associated toxicities such as CRS and immune effector cell–associated neurotoxicity syndrome (ICANS). CRS, reported in approximately 70–90% of treated patients with severe grades in 10–30% depending on tumour type and CAR construct, is driven by a complex cytokine network rather than CAR T- cells alone [64, 65]. Transcriptomic profiling reveals that myeloid cells and macrophages are major producers of inflammatory mediators including Interleukin 6 (IL6), Interleukin 1β (IL-1β), and Granulocyte-Macrophage Colony-Stimulating Factor (GM CSF), which correlate with clinical severity [67]. Predictive models using genomic signatures enable clinicians to identify patients at elevated risk and intervene early with agents like IL 6 receptor antagonists or IL 1 blockade, significantly mitigating life threatening symptoms without compromising antitumor activity [68]. By integrating genomics into toxicity prediction, therapeutic management becomes more precise and personalized, optimizing patient safety.

Genomic Mechanisms of Resistance and Relapse

Despite the high initial response rates, relapse remains a significant challenge in CAR T therapy, affecting 20–40% of patients in CD19 targeted treatment cohorts [70, 71]. Genomic analyses have

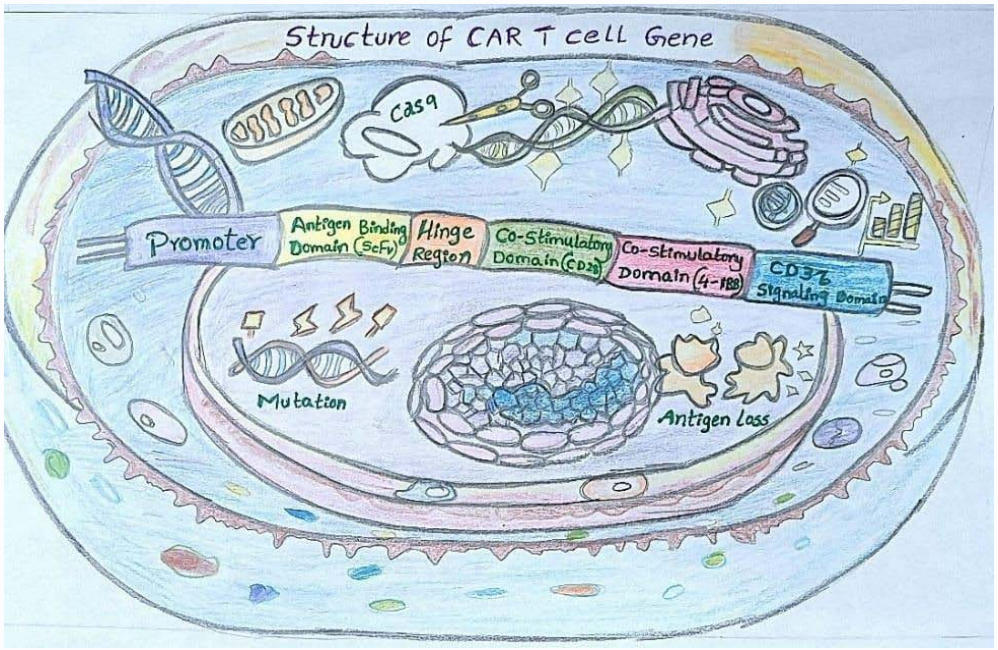

Figure 2: Structure of a CAR T- cell gene.

elucidated key mechanisms behind resistance and relapse, including antigen loss through mutation or alternative splicing, lineage switching, and epigenetic silencing that prevent CAR T recognition [39, 42, 72]. Tumour cells may also develop defects in interferon response and apoptotic pathways, diminishing the downstream effects of CAR T cytotoxicity [34, 73]. Functional genomic CRISPR screens have identified tumour intrinsic resistance genes whose perturbation restores sensitivity, providing a rationale for combining CAR T with targeted agents or engineering dual target constructs that reduce the likelihood of antigen escape [74, 75, 81]. This genomic understanding enables clinicians and researchers to anticipate and counteract resistance mechanisms, extending the durability of responses.

Bioinformatics and Artificial Intelligence in CAR T Genomics

The breadth and complexity of genomic data generated from CAR T research require advanced bioinformatics and artificial intelligence (AI) for meaningful interpretation. Machine learning models that integrate genomic, transcriptomic, and clinical features have shown increasing accuracy in predicting therapeutic response, toxicity risk, and relapse potential [76, 77]. AI based single cell analyses can identify rare but clinically relevant cell subpopulations that correlate with long term remission or early exhaustion, thereby guiding construct optimization and patient stratification [78]. Predictive algorithms are also being designed to tailor lymphodepletion regimens and CAR dosing in real time, establishing a foundation for dynamic, precision immunotherapy paradigms [79]. These computational approaches are essential for translating genomic insights into actionable clinical strategies.

Clinical Implications for Patient Safety and Therapeutic Efficacy

When integrated across the CAR T workflow from antigen selection and construct design to toxicity prediction and longitudinal monitoring genomics fundamentally improves patient safety and therapeutic effectiveness. Genomics guided antigen selection minimizes off tumour risks, while predictive biomarkers and genomic monitoring anticipate adverse events and relapse, allowing timely intervention [31, 35, 38]. Genome edited CAR constructs engineered for improved persistence and reduced exhaustion demonstrate higher complete response rates and prolonged progression free survival in multiple treatment settings [36, 47, 63]. These combined genomic advances are catalysing a shift toward truly personalized cancer immunotherapy, enhancing sustained remission and quality of life for patients with refractory malignancies.

Patient Safety in CAR T- cell Therapy

The clinical success of CAR T- cell therapy is accompanied by a distinct toxicity profile resulting from intense immune activation, making patient safety a central concern in both research and clinical practice. Data from pivotal clinical trials and large real-world studies, including ZUMA-1, JULIET, ELIANA, and TRANSCEND NHL 001, indicate that treatment-related adverse events occur in approximately 70–95% of patients, emphasizing the need for robust safety monitoring and risk mitigation strategies [64, 67].

Among these toxicities, cytokine release syndrome (CRS) represents the most common complication. Across CD19-targeted CAR T trials, CRS has been reported in 70–90% of treated patients, with severe manifestations (grade ≥3) occurring in 10–30% of cases [64, 69]. In the ZUMA-1 trial evaluating axicabtagene ciloleucel, high-grade CRS was observed in ~13% of patients, whereas the JULIET trial of tisagenlecleucel reported severe CRS rates of approximately 22% [64, 65]. Comparative clinical and genomic analyses demonstrate that CAR constructs incorporating CD28 co-stimulatory domains tend to induce earlier and more intense cytokine release, while 4-1BB-based constructs are associated with delayed onset and prolonged immune activation [66, 67].

Transcriptomic investigations from both clinical samples and preclinical models have revealed that CRS is largely driven by host myeloid cells, rather than CAR T- cells directly. Studies by Norelli

et al. [45] identified early induction of IL6, IL1B, Interferon-gamma (IFNG), Tumour Necrosis Factor (TNF), and GMCSF-related gene programs as key molecular correlates of CRS severity [68, 71]. These findings provided the mechanistic rationale for cytokine-directed interventions, and predictive genomic models based on these signatures have achieved 70–85% sensitivity for identifying patients at risk of severe Cytokine Release Syndrome (CRS) prior to symptom onset [72].

Immune effector cell–associated neurotoxicity syndrome (ICANS) is another major safety concern, affecting 20–60% of patients, with grade ≥3 events reported in 10–25% of cases across major trials [64, 67, 73]. Higher incidences of severe ICANS have been reported in CD28-based CAR T products, such as in ZUMA-1, where rates approached 28%, compared with lower frequencies observed in 4-1BB-based therapies [65, 73]. Transcriptomic profiling of cerebrospinal fluid and peripheral blood by Gust et al. (47). has linked ICANS to endothelial dysfunction, disruption of the blood brain barrier, and inflammasome activation [74, 76]. Notably, these molecular changes can be detected 3–5 days before clinical neurotoxicity, supporting the role of genomics in early risk prediction [75, 76].

While on-target, off-tumour toxicity is uncommon in currently approved CD19 and B-cell maturation antigen (BCMA) CAR T therapies, it remains a critical consideration during target development. Previous clinical experiences with Human Epidermal Growth Factor Receptor 2 (HER2) - and Molecular Imaging of CAR-T Cell Therapy or Imaging the CAR-T therapy in vivo (MAGE) -directed T cell therapies demonstrated fatal toxicities caused by unrecognized antigen expression in normal tissues [77, 78]. The widespread adoption of bulk and single-cell transcriptomic atlases has substantially reduced this risk, contributing to the low incidence (<5%) of severe non-haematologic organ toxicity reported with approved CAR T products [79, 80].

Long-term follow-up studies and post-marketing surveillance indicate that secondary malignancies and insertional oncogenesis are rare, with reported incidences below 1% [59, 81]. Next-generation sequencing–based integration site analyses consistently reveal polyclonal CAR T- cell expansion, particularly in patients achieving durable remission, thereby mitigating concerns regarding clonal dominance and genomic instability [59, 82]. Clinical outcome analyses further demonstrate that persistence of CAR T- cells beyond 6–12 months is associated with prolonged progression-free survival, whereas early loss of CAR T- cells correlates with relapse rates exceeding 40% within two years [69, 78].

Advances in genome engineering have further enhanced CAR T safety. Targeted insertion of CAR constructs into defined genomic loci, such as the TRAC locus, reduces tonic signalling and limits T cell exhaustion, as demonstrated in early clinical studies by Eyquem et al. [59]. Additionally, inducible safety mechanisms, including iCasp9-based suicide switches, enable rapid elimination of CAR T-cells, achieving >90% cell clearance within hours when activated and providing an effective safeguard against uncontrollable toxicity [60, 66].

Overall, the integration of genomics has shifted CAR T- cell therapy toward a proactive safety framework, enabling early toxicity prediction, rational construct design, and real-time monitoring. These advances support safer clinical implementation while preserving the potent antitumour efficacy of CAR T- cell therapies.

Limitations and Future Perspectives

Limitations

Despite the clinical success of CAR T-cell therapy in haematological malignancies, several biological, technical, and logistical limitations remain. Tumour antigen heterogeneity and ongoing genomic instability allow malignant subclones to downregulate or completely lose target antigen expression, leading to immune escape and disease relapse [65, 67]. Single-cell genomic analyses have demonstrated that antigen-negative populations may pre-exist prior to therapy and expand under selective pressure following CAR T-cell infusion [44].

Another major limitation is the complex, time-intensive, and costly nature of autologous CAR T-cell manufacturing. Variability in starting T-cell quality, prolonged vein-to-vein time, and manufacturing failures in heavily pre-treated patients, and high production costs significantly limit widespread clinical accessibility [64, 73]. These delays can be particularly detrimental for patients with rapidly progressing or refractory disease.

Additionally, the immunosuppressive tumour microenvironment (TME) presents a substantial barrier, particularly in solid tumours. Regulatory T cells, myeloid-derived suppressor cells, inhibitory cytokines such as TGF-β and IL-10, hypoxia, and dense stromal architecture impair CAR T-cell trafficking, expansion, and cytotoxic activity [14, 72]. Transcriptomic profiling of solid tumours has revealed upregulation of immune-evasion pathways that blunt CAR T-cell function even in the presence of adequate antigen recognition [68].

Future Perspectives

Emerging strategies aim to overcome these limitations through the integration of advanced genomics, multi-omics profiling, and next-generation cellular engineering. Multi-omics approaches, combining genomics, transcriptomics, epigenomics, and proteomics at single-cell resolution, enable precise identification of patient-specific targets and resistance mechanisms, supporting rational CAR design and adaptive treatment strategies [74, 76].

The development of allogeneic "off-the-shelf" CAR T-cell therapies represents a promising avenue to address manufacturing and accessibility challenges. Genome-editing technologies such as CRISPR/Cas9 are being used to disrupt endogenous T-cell receptors and HLA (Human Leukocyte Antigen) molecules, thereby reducing graft-versus-host disease and host immune rejection [77, 78]. Early clinical studies suggest that these approaches may significantly shorten treatment timelines while maintaining therapeutic efficacy.

In parallel, genome-edited "armored" CAR T- cells engineered to resist exhaustion and suppressive signalling are demonstrating enhanced durability. Strategies including Programmed Cell Death Protein 1 (PD1) disruption, cytokine armouring (e.g., IL-12 or IL-18 secretion), and transcriptional reprogramming improve CAR T-cell persistence and antitumour activity within hostile tumour microenvironments.

Finally, the integration of single-cell genomics with artificial intelligence (AI) and machine-learning frameworks is expected to transform CAR T therapy into a dynamic, precision-guided intervention. AI-driven models that integrate genomic, transcriptomic, and clinical data can predict therapeutic response,

toxicity risk, and relapse, enabling real-time treatment optimization and personalized dosing strategies [81].

Conclusion

CAR T cell therapy has established itself as a transformative approach in the treatment of haematological malignancies, offering durable remissions in patients with otherwise refractory disease. The integration of genomics into CAR T cell research has provided unprecedented insights into tumour heterogeneity, antigen expression, and immune evasion, enabling the identification of novel, tumour-specific targets while minimizing off-tumour toxicity. Genomic technologies, including next-generation sequencing, transcriptomics, and single-cell analyses, have also allowed for patient-specific stratification, early detection of minimal residual disease, and monitoring of clonal evolution, enhancing the precision of treatment planning. Furthermore, functional genomics and CRISPR-mediated gene editing have facilitated the rational design of next-generation CAR constructs with improved persistence, reduced exhaustion, and enhanced cytotoxic potency.

Despite these advances, challenges such as antigen loss, tumour microenvironment immunosuppression, manufacturing complexity, and high cost continue to limit the broader application of CAR T cell therapy, particularly in solid tumours. Future strategies focusing on allogeneic "off-the-shelf" CAR T- cells, armored constructs resistant to inhibitory signals, and multi-omics-guided engineering are poised to address these barriers. The convergence of genomics, single-cell technologies, and artificial intelligence promises real-time monitoring, adaptive treatment optimization, and fully personalized immunotherapy.

In conclusion, genomics has fundamentally reshaped CAR T cell therapy by providing mechanistic insights and enabling precision engineering. Continued integration of genomic innovations with cellular engineering strategies is expected to expand the therapeutic potential of CAR T- cells, ultimately improving outcomes for patients with both haematological and solid tumours.

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