

Review

Mechanisms of Action of Ready-to-Use Therapies in Hematologic Malignancies: From Clinical Impact to Future Directions

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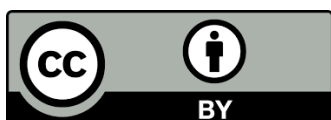
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Abstract

Off-the-shelf cellular therapies, utilizing allogeneic T cells derived from healthy donors, represent a promising alternative to autologous chimeric antigen receptor T-cell (CAR-T) therapies for the treatment of hematological malignancies such as leukemias and lymphomas. Unlike autologous approaches, which require the patient's own cell collection, modification, and expansion, off-the-shelf therapies can be prepared in advance, substantially reducing treatment timelines, decreasing costs, and improving global accessibility. Recent technological advancements, including gene-editing techniques such as CRISPR-Cas9, HLA-



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matching strategies, and next-generation CAR-T cell designs, have been pivotal in overcoming limitations such as immune rejection and graft-versus-host disease. Alternative cellular sources such as umbilical cord blood and induced pluripotent stem cells are also being explored to enhance scalability and compatibility. However, ethical concerns related to donor cell sourcing and the use of gene-editing technologies must be addressed to ensure responsible clinical implementation. This review outlines the mechanisms, recent advances, challenges, ethical issues, and prospects of off-the-shelf cellular therapies, emphasizing their transformative potential in cancer immunotherapy.

Keywords

Allogeneic CAR-T cells; hematological malignancies; chimeric antigen receptor T cells; graft-versus-host disease; immunotherapy; CRISPR-Cas9

1. Introduction

Hematological malignancies, such as leukemias and lymphomas, are a diverse group of cancers that affect the blood and lymphatic systems, and continue to present significant therapeutic challenges [1-4]. Over the past decade, chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized treatment for patients with relapsed or refractory disease [5, 6]. However, most CAR-T products are autologous, requiring individualized cell harvesting, genetic modification, and expansion. This process is not only time-intensive but also cost-prohibitive, with production delays of 3–6 weeks and high expenses associated with personalized manufacturing infrastructure, making these therapies inaccessible for many patients, especially in low-resource settings.

Off-the-shelf CAR-T therapies aim to overcome these limitations by employing allogeneic T cells obtained from healthy donors. These cells are genetically edited to enhance their anti-tumor activity and minimize immunogenicity, enabling their use in multiple patients without the need for personalization [7, 8]. Gene-editing tools such as CRISPR-Cas9 play a key role in eliminating T cell receptors (TCRs) and HLA molecules, thereby reducing the risk of graft-versus-host disease (GVHD) and immune rejection [9, 10]. Nonetheless, these gene-editing approaches also raise safety concerns, including potential off-target effects and immune responses to Cas9 proteins.

In addition to conventional allogeneic T cells, alternative cell sources are under active investigation. Umbilical cord blood-derived T cells offer immunological naivety and reduced GVHD risk [11], while induced pluripotent stem cells (iPS) provide a renewable and highly modifiable source of therapeutic cells [12]. Natural killer (NK) cells engineered with CARs (CAR-NK) have also emerged as promising candidates, offering a lower risk of GVHD and cytokine release syndrome compared to CAR-T cells [13, 14].

This review examines the key mechanisms, clinical applications, innovations, and ethical implications of off-the-shelf cellular therapies in hematologic malignancies, highlighting how these strategies could complement or surpass current autologous approaches in terms of speed, accessibility, and long-term viability.

2. Mechanisms of Action of Ready-to-Use Therapies

Ready-to-use (off-the-shelf) cellular therapies primarily involve the use of allogeneic T cells derived from healthy donors, engineered to recognize and eliminate cancerous cells [15]. The fundamental mechanism underlying these therapies involves modifying donor T cells through genetic engineering to express chimeric antigen receptors (CARs), synthetic receptors designed to target tumor-associated antigens on malignant cells specifically. Upon infusion into the patient, CAR-T cells selectively bind to cancer cells, inducing targeted cytotoxicity and tumor regression (Figure 1).

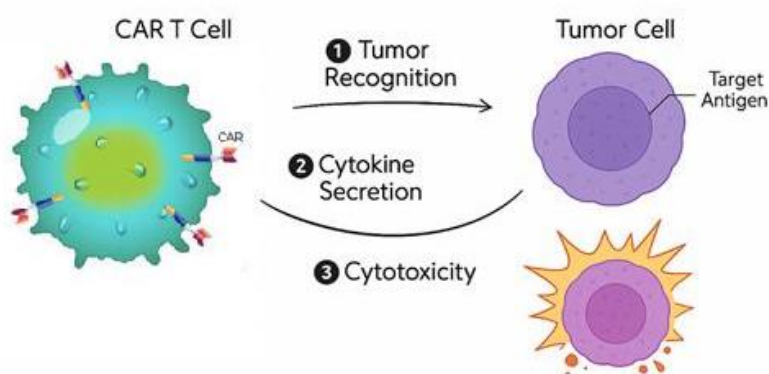


Figure 1 Mechanisms of Action of CAR-T Cells.

Unlike autologous CAR-T cells, which necessitate patient-specific cell harvesting, genetic modification, and ex vivo expansion, off-the-shelf therapies employ cells that are pre-prepared and readily available for immediate use. Donor-derived T cells undergo isolation, laboratory-based expansion, and genetic modifications designed to enhance anti-tumor activity, extend in vivo persistence, and minimize immunogenicity. The cells are genetically edited using advanced gene-editing technologies (Figure 2) such as CRISPR-Cas9 [9], zinc-finger nucleases (ZFNs) [16], or transcription activator-like effector nucleases (TALENs) [17]. CRISPR-Cas9 is particularly prominent due to its precision, versatility, and efficiency in removing immunogenic elements such as TCRs, thus significantly reducing the risks of GVHD and immune rejection.

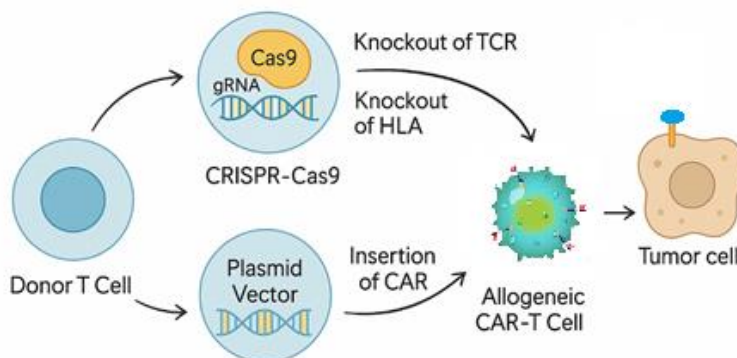


Figure 2 Gene Editing Strategies in Allogeneic CAR-T Cell Manufacturing.

However, the use of CRISPR-Cas9 raises specific safety concerns, primarily due to potential off-target genetic alterations and unintended immune reactions triggered by residual Cas9 proteins. Addressing these concerns is critical for ensuring clinical safety and efficacy, prompting ongoing research into high-fidelity editing enzymes, improved delivery methods, and comprehensive off-target analysis.

Alternative cell sources, including umbilical cord blood cells and induced pluripotent stem cells (iPS), are also being explored to overcome the limitations associated with conventional donor-derived T cells. Umbilical cord blood cells offer advantages, such as reduced risk of GVHD due to their immunologically naïve status. In contrast, iPS-derived T cells provide an essentially unlimited source of standardized, genetically modifiable cells, facilitating broader scalability and consistency of therapeutic products [18]. Among emerging strategies to further enhance the persistence and function of T cells, epigenetic modulation using dCas9-based tools is gaining attention at the preclinical level.

Furthermore, natural killer (NK) cells engineered with CAR-NK have emerged as a promising alternative or complementary approach to traditional CAR-T therapies [19, 20]. CAR-NK cells inherently possess potent cytotoxic capabilities, a reduced likelihood of causing GVHD, and minimal risks of cytokine-release syndrome, highlighting their potential in mitigating several limitations encountered by CAR-T therapies.

Collectively, these advancements highlight the complex yet promising mechanisms underlying ready-to-use cellular therapies, paving the way for broader applicability and improved outcomes in the treatment of hematological malignancies. Among the most promising of these alternatives, CAR-engineered NK cells have attracted growing attention due to their unique immunological features.

While CAR-T cells have shown remarkable efficacy in various hematologic malignancies, CAR-NK cells offer distinct advantages rooted in their innate immune profile. Unlike T cells, natural killer (NK) cells recognize stressed or malignant cells without prior antigen sensitization and are less likely to cause graft-versus-host disease (GVHD), even when used allogeneically. This GVHD-free profile enables more straightforward allogeneic use, avoiding the need for TCR knockout or extensive HLA editing [21].

From a mechanistic perspective, CAR-NK cells combine the advantages of CAR-mediated antigen recognition with intrinsic NK cytotoxicity pathways, including granzyme/perforin release [22, 23] and antibody-dependent cellular cytotoxicity (ADCC) [24], potentially enabling synergistic anti-tumor effects. Moreover, CAR-NK cells tend to produce lower levels of pro-inflammatory cytokines, such as IL-6, which significantly reduces the risk of severe cytokine release syndrome (CRS) and neurotoxicity, common adverse events in CAR-T therapy [25].

However, a key limitation of CAR-NK cells remains their limited *in vivo* persistence, as NK cells typically have shorter half-lives than T cells. Strategies such as the inclusion of cytokine support (e.g., IL-15) within the CAR construct are under development to overcome this issue [26].

Clinical trials have begun to demonstrate the clinical feasibility and efficacy of CAR-NK products. Notably, FT596, an off-the-shelf, iPSC-derived CAR-NK cell product targeting CD19, has shown promising results in a Phase I trial (NCT04245722), with early response rates exceeding 60% in patients with relapsed/refractory B-cell malignancies and a favorable safety profile with no GVHD or high-grade CRS observed [27]. Another candidate, NKX101, a CAR-NK cell targeting NKG2D ligands in AML and MDS (NCT04623944), has also demonstrated early signs of efficacy and safety in initial clinical phases [28].

These data suggest that CAR-NK therapies may represent a safer and potentially more accessible alternative or complement to CAR-T cells, especially in populations at higher risk for toxicity or where rapid availability is essential. Continued optimization of persistence, expansion strategies, and head-to-head comparisons with CAR-T therapies will be crucial in defining their role in the evolving immunotherapy landscape.

3. Advantages of Off-the-Shelf Therapies

Off-the-shelf cellular therapies present numerous compelling advantages over traditional autologous CAR-T therapies, especially regarding treatment accessibility, cost-efficiency, and timeliness (Table 1). A primary advantage is the considerable reduction in preparation and manufacturing times [29]. Autologous CAR-T therapies necessitate extensive, patient-specific cell collection, genetic manipulation, and ex vivo expansion, typically requiring weeks to months before treatment administration. Conversely, off-the-shelf therapies utilize pre-manufactured, donor-derived T cells readily available for immediate infusion, significantly shortening the treatment timeline. This rapid availability is crucial for patients with aggressive hematological malignancies, as timely intervention can significantly impact clinical outcomes.

Table 1 Key Advantages of Off-the-Shelf vs Autologous CAR-T Cell Therapies.

Parameter	Autologous CAR-T Therapy	Off-the-Shelf CAR-T Therapy
Availability	Requires weeks to months for manufacturing and delivery	Immediately available upon clinical need
Production Process	Patient-specific: leukapheresis, gene modification, expansion	Pre-manufactured from healthy donors
Time to Treatment	Delayed due to individual processing	Significantly reduced, enabling rapid intervention
Cost	High, due to personalized procedures and infrastructure	Lower, thanks to standardized and scalable production
Accessibility	Limited in low-resource or high-demand settings	Broader accessibility, including underserved regions
Scalability	One product per patient	Multiple doses per donor; pooled inventories enable broad use
Clinical Impact	It may be delayed for aggressive disease	Ideal for urgent treatment scenarios

Another significant advantage pertains to cost-effectiveness. Autologous CAR-T treatments incur substantial expenses associated with personalized cell harvesting, specialized processing, and individualized manufacturing. These patient-specific procedures substantially increase overall treatment costs, restricting access, particularly in economically constrained healthcare systems. In contrast, off-the-shelf therapies circumvent individual cell processing steps, thus dramatically lowering production costs. By standardizing and streamlining manufacturing processes, off-the-shelf approaches promise enhanced affordability, expanding the availability of advanced therapies

to a broader patient demographic, including underserved populations and resource-limited regions [30].

Additionally, off-the-shelf therapies exhibit enhanced scalability compared to autologous methods. Although production per individual donor remains relatively limited, typically around 10 therapeutic units per healthy donor, the collective availability from multiple donors enables the development of a more extensive therapeutic inventory. This pooled resource strategy can significantly increase the total quantity of therapeutic products available, facilitating broader distribution and timely treatment administration across diverse patient populations globally.

In summary, while both autologous and allogeneic CAR-T therapies require similar manufacturing steps—including gene editing, quality control, and cryopreservation—off-the-shelf cellular therapies offer the advantage of cost amortization across multiple treatment units, typically ten or more per donor. This contributes to reduced treatment preparation time, lower per-unit costs, and improved scalability, addressing key limitations of autologous CAR-T therapies and highlighting the transformative potential of allogeneic approaches for hematological malignancies [31-33].

4. Clinical Applications and Recent Outcomes

Off-the-shelf cellular therapies, notably engineered allogeneic CAR-T cells, have demonstrated promising clinical outcomes in recent studies targeting various hematological malignancies, including leukemias and lymphomas. Clinical trials involving these therapies have shown significant potential, particularly for patients with refractory or relapsed diseases who lack access to autologous CAR-T therapies due to limited viable patient T-cell availability or rapidly progressing disease.

Recent clinical outcomes highlight notable successes in early-phase trials evaluating off-the-shelf CAR-T cells for B-cell malignancies. For example, clinical trials utilizing UCART19 reported encouraging efficacy in pediatric and adult populations with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL), demonstrating complete remission rates ranging from 60% to 80% [29]. Similarly, clinical studies of ALLO-501 for large B-cell lymphoma and follicular lymphoma have shown objective response rates of approximately 60%, with durable responses lasting several months to over a year in a subset of patients [7].

In comparison, autologous CAR-T therapies, despite their personalized nature and historically higher remission rates (ranging from 70% to 90% in various studies), are limited by significantly longer production times, typically 3 to 6 weeks, potentially delaying critical treatment interventions [34]. By contrast, off-the-shelf products, available for immediate administration, have the crucial advantage of rapid treatment initiation, significantly benefiting patients with aggressive malignancies who cannot afford treatment delays.

Data from early-phase studies evaluating products such as PBCAR0191 in chronic lymphocytic leukemia (CLL) and other B-cell malignancies further support their clinical relevance, with early signs of efficacy reported in approximately 50% of relapsed/refractory cases. These outcomes demonstrate that off-the-shelf therapies can provide viable alternatives, particularly when autologous approaches are impractical or infeasible [35].

Although promising, these therapies continue to face challenges, notably regarding durability and long-term persistence in patients. Continuous clinical assessment and rigorous comparative

trials against established autologous CAR-T therapies are essential to fully elucidate their comparative efficacy, optimal use cases, and long-term therapeutic potential.

5. Technological Innovations and Future Directions

The evolution of off-the-shelf cellular therapies is significantly driven by technological innovations aimed at improving efficacy, safety, and broad applicability (Table 2). Central to these advancements is the ongoing refinement of gene-editing technologies, such as CRISPR-Cas9, which enable precise genomic modifications to enhance therapeutic potential and minimize adverse effects. CRISPR-Cas9 facilitates targeted edits to eliminate immunogenic factors, such as human leukocyte antigen (HLA) molecules and T-cell receptors [36].

Table 2 Technological Innovations in Off-the-Shelf Cellular Therapies.

Technology/Strategy	Main Applications	Development Stage	Key Advantages	Current Limitations/Challenges
CRISPR-Cas9 Gene Editing	Knockout of TCR, HLA; insertion of CAR genes	Clinical trials (Phase I/II)	High precision; enables multiplex editing; reduces GVHD and rejection risks	Off-target effects, genomic instability, risk of oncogenesis, long-term safety unknown
Bispecific CAR-T Cells	Targeting multiple tumor antigens simultaneously	Preclinical to Phase I	Reduces antigen escape; improves tumor recognition	Increased complexity; risk of off-tumor toxicity; need for antigen selection refinement
Epigenetic Modulation (via CRISPR/dCas9)	Enhancing T cell persistence and memory formation	Preclinical	Reversible gene expression control; supports functional durability	Technical complexity, limited in vivo validation, and potential unintended gene regulation
iPS-Derived CAR-T Cells	Scalable, standardized source of therapeutic T cells	Early clinical/preclinical	Unlimited expansion; multiple modifications possible; high consistency	Complex differentiation protocols; risk of residual pluripotent cells (tumorigenicity)
Umbilical Cord Blood-Derived T Cells	Alternative donor source with reduced immunogenicity	Clinical studies ongoing	Naïve immune profile; lower GVHD risk	Limited cell numbers per unit; slower expansion compared to adult cells
CAR-NK Cells	GVHD-free cytotoxic cell therapy, particularly in high-risk or elderly populations	Phase I/II trials	No GVHD; lower CRS risk; natural killing capacity	Short in vivo persistence; requires cytokine support (e.g., IL-15)

GVHD: Graft-versus-Host Disease; CRS: Cytokine Release Syndrome; iPS: Induced Pluripotent Stem; TCR: T Cell Receptor; HLA: Human Leukocyte Antigen.

The use of CRISPR-Cas9 in clinical-grade products raises significant safety concerns, including the risk of off-target effects, genomic instability, and unintended mutations that could lead to oncogenic transformation or altered cellular behavior. These issues underscore the need for stringent validation protocols and long-term follow-up studies to ensure the safe implementation of gene-edited allogeneic therapies in clinical practice [37].

In parallel, next-generation CAR-T cell therapies are being developed to broaden the scope of treatable malignancies and enhance therapeutic durability. Strategies involving CRISPR-Cas9-based genome editing offer the potential to improve CAR-T cell persistence by modulating their epigenetic landscape. In addition, this technology enables the simultaneous knock-out of genes such as TCR and HLA, thereby reducing alloreactivity and immunogenicity, and further improving the overall performance of CAR-T cells [38, 39].

Alternative cellular sources, including iPS-derived T cells and umbilical cord blood cells, are gaining attention due to their unique advantages. iPS-derived T cells offer an inexhaustible and uniform source of therapeutic cells, enabling greater scalability, standardized production, and the incorporation of multiple genetic modifications. Umbilical cord blood cells offer immunological advantages, notably a reduced risk of GVHD, making them an attractive source for clinical use.

CAR-NK cell therapies are also emerging as critical alternatives or complementary treatments to conventional CAR-T cell therapies. CAR-NK cells inherently possess robust antitumor activity, lack GVHD potential, and present lower risks of severe cytokine release syndrome, highlighting their potential advantages in clinical scenarios requiring a safer immunotherapeutic approach.

Future research directions must include rigorous clinical validation of these innovative approaches, continued assessment of their comparative effectiveness against existing therapies, and overcoming persistent challenges related to immune compatibility and long-term safety. The integration of novel technologies, such as advanced gene-editing techniques, epigenetic modulation, and alternative cell sources, promises to significantly broaden the therapeutic landscape and accessibility of off-the-shelf cell therapy [40-43].

6. Clinical Trials: Ongoing and Completed

Several clinical trials, both ongoing and completed, are evaluating the safety, efficacy, and feasibility of off-the-shelf CAR-T cell therapies in hematologic malignancies (Table 3). These studies have provided critical insights into the therapeutic potential of allogeneic approaches and are helping to shape the future landscape of adoptive cellular immunotherapy.

Table 3 Comparative Clinical Outcomes of Autologous vs Allogeneic CAR-T Therapies in B-cell Malignancies.

Parameter	Autologous CAR-T (e.g., Axi-cel, Tisa-cel)	Allogeneic CAR-T (e.g., ALLO-501, UCART19)
Overall Response Rate (ORR)	70–90%	60–75%
Complete Response Rate (CR)	40–60%	30–50%
Median Progression-Free Survival (PFS)	6–12 months	3–6 months
Median Overall Survival (OS)	12–24+ months	6–12 months
1-year OS Rate	~60–70%	~45–55%

Cell Persistence (detectable at 6 mo)	>60%	<30%
GVHD Incidence	Rare (self-derived)	0–20% (depends on TCR knockout strategy)
Cytokine Release Syndrome (CRS)	Grade ≥ 2 : 30–50%	Grade ≥ 2 : 10–25%
Neurotoxicity	10–30%	<10%

ORR: Overall Response Rate; CR: Complete Response; PFS: Progression-Free Survival; OS: Overall Survival; GVHD: Graft-versus-Host Disease; CRS: Cytokine Release Syndrome.

One of the most extensively studied products is UCART19, an anti-CD19 allogeneic CAR-T therapy derived from healthy donors. Two phase 1 trials (NCT02746952 and NCT02808442) conducted in pediatric and adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) have demonstrated complete response (CR) rates between 60% and 80%, with manageable safety profiles. Notably, these responses occurred without the need for patient-specific manufacturing, highlighting the logistical advantage of allogeneic approaches [29].

Similarly, ALLO-501, developed to target CD19 in large B-cell lymphoma and follicular lymphoma, has shown encouraging results in the ALPHA trial (NCT03939026). An overall response rate (ORR) of approximately 60% was observed, with a subset of patients achieving durable remissions extending beyond 12 months. The ALPHA2 trial (NCT04416984), which evaluates a next-generation version, ALLO-501A, in relapsed/refractory settings, is currently ongoing and shows comparable early outcomes [7, 44].

The PBCAR0191 trial (NCT03666000) explores a different allogeneic anti-CD19 platform in patients with B-cell malignancies, including chronic lymphocytic leukemia (CLL). Interim results from this phase 1 study report an ORR of ~50%, including patients with heavily pretreated and chemotherapy-refractory disease [45].

While these findings confirm the clinical feasibility of off-the-shelf CAR-T products, challenges related to long-term persistence and durability of response remain. Unlike autologous CAR-T therapies, where persistence beyond 6 to 12 months has been correlated with prolonged remission, some allogeneic products show declining efficacy over time due to immune-mediated clearance.

Future clinical trials should aim to compare autologous and allogeneic CAR-T therapies head-to-head, using standardized endpoints such as progression-free survival (PFS), overall survival (OS), and long-term toxicity. Moreover, combining allogeneic CAR-T cells with immune checkpoint inhibitors or immunosuppressive conditioning regimens may improve engraftment and persistence.

These trials highlight the potential of off-the-shelf therapies to redefine the standard of care for hematologic cancers, particularly for patients who cannot access or tolerate autologous CAR-T treatment. Continued clinical validation will be essential to define their optimal use and long-term positioning in the field of hematology-oncology.

7. Ethical Considerations

As off-the-shelf cellular therapies advance toward broader clinical use, ethical considerations become increasingly critical to ensure responsible innovation and equitable patient care. One primary ethical concern relates to the sourcing of allogeneic cells. Donor cells used to generate therapeutic products must be obtained with fully informed consent, ensuring that donors are aware of the potential future applications of their biological materials. Issues of donor anonymity, privacy,

and the long-term use of stored biological samples must be managed with strict ethical safeguards [46].

Genetic modification of human cells, particularly using powerful tools like CRISPR-Cas9, also raises ethical concerns regarding unintended consequences, heritable changes, and long-term safety implications. Although off-the-shelf therapies do not involve germline editing, the use of genome-editing tools in therapeutic contexts must be governed by strict ethical frameworks to minimize risks and maintain public trust. The potential for off-target effects and unforeseen biological responses further underscores the need for ethical oversight [47].

Equity in access is another crucial ethical dimension. The scalability and cost-efficiency of off-the-shelf therapies promise wider global availability; however, disparities in healthcare infrastructure and regulatory environments could limit access in underserved regions. Policymakers and stakeholders must collaborate to ensure that these advanced therapies are accessible to patients, irrespective of their socioeconomic status or geographic location [48].

Additionally, as commercial interest in cellular therapies grows, ethical oversight is essential to prevent conflicts of interest and ensure that profit motives do not compromise patient safety or research integrity. Transparent reporting of funding sources, clinical outcomes, and adverse events is essential for maintaining scientific accountability and fostering public confidence in these emerging technologies [49].

As the clinical development of off-the-shelf cellular therapies accelerates, alignment with international regulatory standards becomes crucial to ensure safe and equitable access. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidance documents outlining regulatory pathways for advanced therapy medicinal products (ATMPs), including gene-edited and allogeneic cell therapies. However, significant disparities remain in approval processes, manufacturing requirements, and long-term follow-up obligations across different jurisdictions. These inconsistencies can delay global clinical trial designs, hinder cross-border collaboration, and ultimately limit patient access to innovative therapies [50].

To address these challenges, a coordinated global effort toward regulatory harmonization is urgently needed. International collaborations—such as those led by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) or the World Health Organization (WHO)—could facilitate standardized frameworks for product evaluation, pharmacovigilance, and risk mitigation. Moreover, regulatory convergence would support the development of global clinical trials and equitable distribution of therapeutic, particularly in low- and middle-income countries where access barriers are most profound.

Overall, ethical considerations and regulatory alignment must remain at the forefront of the development and implementation of off-the-shelf cellular therapies, guiding decisions around donor consent, patient safety, global equity, and responsible innovation.

8. Conclusions

Off-the-shelf cellular therapies, particularly those utilizing genetically modified allogeneic T cells, represent a transformative innovation in the treatment of hematological malignancies. By addressing key limitations of autologous CAR-T cell therapies, such as high costs, limited scalability, and delayed treatment timelines, these therapies offer a compelling alternative with broader accessibility and potential for global impact.

Advances in gene-editing technologies, notably CRISPR-Cas9, and alternative cell sources, such as induced pluripotent stem cells (iPS cells) and umbilical cord blood, have expanded the therapeutic toolkit available for developing safe and effective allogeneic products. Next-generation platforms, including bispecific CAR-T cells, epigenetically enhanced T cells, and CAR-NK cells, continue to push the boundaries of what is possible in cellular immunotherapy.

Clinical trials have begun to demonstrate the feasibility and efficacy of off-the-shelf approaches, with encouraging response rates and manageable safety profiles in patients with relapsed or refractory malignancies. However, long-term persistence and immune compatibility remain active areas of investigation. Rigorous comparative trials, regulatory oversight, and ethical scrutiny will be essential to integrate these therapies into standard clinical practice fully.

Ultimately, off-the-shelf cellular therapies offer a promising path forward in the evolution of cancer treatment. Through continued innovation, clinical validation, and attention to equity and ethics, these therapies may become a cornerstone of accessible, effective, and personalized cancer care worldwide.

Author Contributions

F.E.L. and F.G. conceived the manuscript structure and supervised its preparation. F.E.L., B.D., and P.P. performed the literature review and wrote the initial draft. A.D. and S.D. contributed to the clinical and translational aspects of allogeneic CAR-T cell therapy. S.M. provided input on the technological innovations and clinical trials. All authors contributed to manuscript revision, read, and approved the final version.

Competing Interests

The authors declare no conflict of interest.

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