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REVIEW ARTICLE

Cell Therapy: A Review of Clinical Applications, Barriers, Emerging Technologies, and Future Perspectives

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Abstract

Cell therapy offers a new horizon for diseases that do not respond adequately to conventional treatments. This approach not only controls symptoms but also targets the underlying causes of disease, aiming to regenerate tissues and restore their function. Cell therapy has been applied in the treatment of cancer, cardiovascular diseases, neurological disorders, autoimmune diseases, resistant infections, infertility, and organ replacement, representing a revolution in managing otherwise intractable conditions. As this therapeutic field is rapidly advancing, with ongoing clinical trials and new research, understanding the latest developments is crucial for the adoption and application of innovative treatment strategies. To provide a comprehensive, structured, and up-to-date overview of cell therapy, an extensive search was conducted in Google Scholar, PubMed, and ClinicalTrials.gov using keywords related to cell therapy. Articles published between 2019 and 2025 were reviewed and analyzed, focusing on clinical applications of stem cells, clinical challenges, and emerging cellular technologies. Clinical studies from 2019–2025 show that cell therapy can achieve meaningful improvements in disease-specific endpoints, with several trials reporting enhanced organ function, reduced disease activity, and favorable safety profiles in carefully selected patient populations. Evidence suggests potential disease-modifying effects, particularly in regenerative and immunomodulatory contexts, though responses vary by cell type and condition. Despite its great potential, cell therapy still faces challenges such as high costs, immunogenicity, limited cell homing, large-scale production difficulties, ethical considerations, and the need for advanced infrastructure. Progress in gene editing, nanotechnology, organoids, bioprinting, and artificial intelligence is expected to facilitate the future development of this field. Although complex, cell therapy represents one of the most promising approaches in modern medicine. Its integration with tissue engineering, gene therapy, and personalized medicine outlines a promising future for the treatment of refractory diseases.

Keywords Cell Therapy, Immunotherapy, Personalized Medicine,Regenerative Medicine

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1 Introduction

The concept of using biological materials for therapeutic purposes dates back to the 19th century, when early experimental attempts were made to transplant tissues and organs in different forms. In 1950, the first successful human organ transplantation was performed.[1,2] During the 1960s, the discovery of bone marrow hematopoietic stem cells (HSCs) and recognition of their potential in treating hematologic disorders paved the way for further advances in regenerative medicine. In 1956, the first successful bone marrow transplantation for the treatment of leukemia and aplastic anemia marked a significant milestone in cell therapy. Later, with progress in molecular biology and genetic engineering, scientists began manipulating cells to enhance their therapeutic properties (Table 1).[3,4]

Table 1 History of Cell Therapy

Year	Milestone	Reference
1956	Successful allogeneic bone marrow transplant in a child with leukemia by E. Donnall Thomas	[3]
1963	Discovery of HSCs by James Till and Ernest McCulloch	[5]
1967	The first successful autologous bone marrow transplant by Robert A. Good.	[3]
1968	First bone marrow transplant with a matched related donor, Dr. Robert A. Good	[6]
1998	Isolation of human ESCs by James Thomson	[7]
2001	First clinical trial of MSCs for treatment of graft-versus-host disease	[8]
2006	Discovery of IPSCs by Shinya Yamanaka	[9]
2017	FDA approval of the first CAR-T cell therapy, Kymriah, for pediatric leukemia	[10]
2010s-2020s	Innovations in Gene Editing (CRISPR/Cas9)	[9]
2022	FDA approval of the first allogeneic off-the-shelf CAR-T cell therapy, Carvykti, for multiple myeloma	[11]
2024	Research into next-generation CAR-T therapies for solid tumors is expanding, while advancements in stem cell therapy enhance treatment quality and scalability	[12, 13]

MSCs: Mesenchymal stem cells
ESCs: Embryonic stem cells
HSCs: Hematopoietic stem cells
IPSCs: Induced pluripotent stem cells
CAR-T cell: Chimeric antigen receptor T-cell
FDA: Food and Drug Administration

Unlike conventional therapies, which primarily manage symptoms, cell therapy targets the root causes of diseases, offering the potential for complete disease resolution. Many chronic and hard-to-treat conditions, such as cancer, heart failure, neurodegenerative disorders, and autoimmune diseases, remain without effective and durable treatments despite significant advances in medical science. This therapeutic gap has made the development of innovative treatment strategies increasingly essential. In this context, cell therapy has emerged as a promising option, aiming to regenerate and replace damaged cells and tissues, thereby fundamentally transforming the therapeutic landscape (Figure 1).[14]

Figure 1 Cell-based therapy in the treatment of various diseases (The Figure is created with BioRender.com, accessed in May 2024)

This article aimed to provide a comprehensive analysis of current advancements and trends in cell therapy, as well as to examine its prospects. This review seeks to integrate existing research findings and offer a cohesive overview of how cell therapy has emerged as a central therapeutic approach in modern medicine.

1. Cell Therapy and Regenerative Medicine

Cells used in regenerative medicine facilitate the replacement or repair of damaged tissues through various growth factors and cytokines, providing a source of healthy cells to substitute for injured ones. For example, in diabetes, insulin-producing beta cells in the pancreas can be replaced with donor-derived islet cells or stem cells for therapeutic purposes.[15] Additionally, cell therapy is being investigated for conditions such as spinal cord injuries, stroke, neurological disorders like Parkinson's disease,[16] myocardial repair in cardiovascular diseases,[17] musculoskeletal injuries, tendon and cartilage repair,[18,19] and organ transplantation.

1.1 Cancer Therapy

Cancer remains one of the leading causes of mortality and a major global health challenge, accounting for substantial annual expenditures on treatment and research for diagnosis and therapy.[20] In oncology, cell therapy is applied as immunotherapy, which harnesses the patient's immune system to target and eliminate cancer cells. By

activating or enhancing the body's immune response against tumors, these therapies have revolutionized the treatment of various cancers.[21] Among the most prominent approaches are chimeric antigen receptor T-cell (CAR-T cell) therapy and tumor-infiltrating lymphocytes (TILs).

CAR-T cell therapy involves genetically modifying a patient's T cells to better recognize and attack cancer cells. T cells are collected from the patient's blood and engineered to express a CAR that specifically binds to antigens on tumor cells. The modified CAR-T cells are expanded in the laboratory and then infused back into the patient, where they seek and destroy cancer cells expressing the target antigen. This approach has proven particularly effective for hematologic malignancies such as certain types of leukemia and lymphoma. Consequently, products like Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) have received Food and Drug Administration (FDA) approval for treating specific blood cancers.

However, applying CAR-T therapy to solid tumors faces multiple challenges, including inhibition by the tumor microenvironment, antigen heterogeneity, immune evasion, physical barriers such as dense extracellular matrices, abnormal vasculature, and off-target toxicity to normal cells due to shared antigens between tumor and healthy cells.[22] Current research focuses on expanding CAR-T applications to solid tumors, improving CAR-T persistence and efficacy, and reducing adverse effects such as cytokine release syndrome (CRS) and neurotoxicity (Figure 2).[23,24]

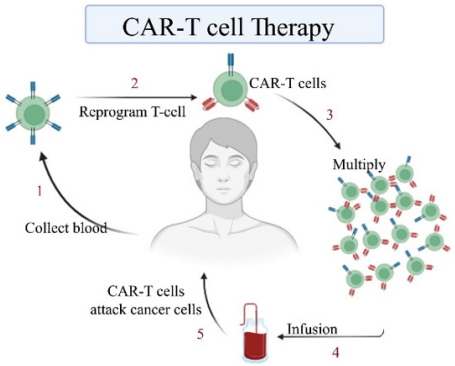

Figure 2 CAR T-cell therapy (The Figure is created with BioRender.com, accessed in May 2024)

T lymphocytes collected from the patient's blood are genetically engineered in the laboratory to specifically recognize and attack the patient's cancer cells. The modified T cells are then reinfused into the patient, where they target and destroy the cancer.

TIL Therapy

TIL therapy represents another form of immunotherapy, utilizing T cells that naturally infiltrate the tumor microenvironment. These TILs are isolated from a patient's tumor tissue, where they are specifically primed against tumor antigens, and then expanded ex vivo, often with interleukin-2 (IL-2) or other growth factors, before being reinfused into the patient. The goal is to enhance the patient's immune response to effectively target and eliminate cancer cells.

TIL therapy has shown promising results, including durable responses, in melanoma and other solid tumors such as cervical and head-and-neck cancers. Ongoing research aims to optimize TIL culture conditions and combine TIL therapy with immune checkpoint inhibitors (e.g., PD-1 or CTLA-4 inhibitors) to improve efficacy. Despite its potential, limitations remain, including time-consuming procedures, the necessity of tumor-specific T cells, challenges in identifying novel tumor antigens, and overcoming the immunosuppressive tumor microenvironment (Figure 3).[25-27]

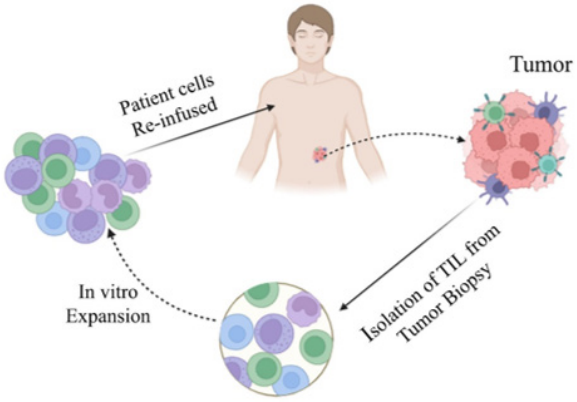

Figure 3 TIL Therapy (The Figure is created with BioRender.com, accessed in May 2024)

T cells infiltrating the tumor are isolated from tumor tissue, expanded in the laboratory, and then reinfused into the patient.

1.2 Cardiovascular Diseases

Unlike conventional therapies for cardiovascular diseases, cell-based treatments have the potential to regenerate heart tissue. This regenerative capacity is particularly important because heart failure often involves irreversible damage to the myocardium, leading to scar formation and impaired blood flow.[28] Recent studies indicate that stem cells can differentiate into cardiomyocytes and secrete paracrine factors that promote cardiac tissue repair and angiogenesis.[29] The therapeutic effects of these cells occur through multiple mechanisms, including direct differentiation into cardiac cells, growth factor secretion, and modulation of immune responses, ultimately contributing to tissue repair and functional recovery of the heart[30,31] Clinical trial

results evaluating the efficacy of cell therapy in acute myocardial infarction, chronic ischemic heart disease, and heart failure have been variable; some studies report improvements in cardiac function and quality of life, while others show limited or inconclusive benefits. This variability can be attributed to factors such as the type of stem cells used, the method of cell delivery, and patient-specific conditions at the time of administration. For instance, intracoronary injection of mesenchymal stem cells (MSCs) has demonstrated potential in improving left ventricular function and reducing scar tissue in patients with ischemic heart disease. However, challenges such as the death of transplanted cells within damaged cardiac tissue remain significant obstacles.[32]

1.3 Autoimmune Disease Therapy

Autoimmune diseases occur when the immune system mistakenly attacks the body's healthy cells and tissues. Current conventional treatments, including immunosuppressants and anti-inflammatory drugs, primarily manage symptoms but are often insufficient to halt underlying autoimmune responses or achieve lasting remission. In cell therapy for autoimmune diseases, dysfunctional immune cells are eliminated using high-dose chemotherapy or irradiation, followed by the infusion of healthy stem cells (from the patient or a donor) to reconstitute a functional immune system.[33]

For example, CAR-T cells play a key role in conditions such as lupus, an autoimmune disease in which B cells produce antibodies against the body. CAR-T cells target and eliminate CD19, a marker specific to B cells, thereby reducing inflammatory responses.[34] Regulatory T cells (T-regs) are also used in cell therapy to maintain immune tolerance and suppress autoimmune responses, with several clinical trials currently evaluating T-reg therapy for autoimmune conditions such as type 1 diabetes and multiple sclerosis (MS).[35]

MSCs represent another cellular source due to their immunomodulatory and regenerative properties. They can suppress inflammation, induce immune tolerance, and enhance tissue repair.[36] Additionally, recent studies have explored the direct injection of neural stem cells (NSCs) into the brains of MS patients, showing preliminary evidence of neuroprotection and enhanced repair, suggesting a potential new therapeutic avenue, particularly for progressive forms of MS.[37]

Differentiation of stem cells into insulin-producing beta cells is another emerging cell therapy approach for diabetes. Embryonic stem cells (ESCs) possess a unique ability to differentiate into any cell type, including insulin-producing beta cells. Recent studies have demonstrated that ESC-derived beta cells function similarly to native pancreatic beta cells, secreting insulin in response to glucose. Achieving functional beta cell clusters with long-term survival remains a key goal in diabetes treatment.[38] Induced pluripotent stem cells (IPSCs), generated by reprogramming adult somatic cells, can similarly differentiate into pancreatic beta cells. This approach offers the advantage of using patient-derived cells, potentially reducing the risk of immune rejection. Research indicates that IPSC-derived beta cells act like endogenous beta cells, secreting insulin in a glucose-dependent manner.[39,40]

Despite their promise, cell therapies for autoimmune diseases face challenges, including identifying suitable cell sources, determining optimal mechanisms to precisely modulate the immune system, managing immune rejection and graft compatibility, and ensuring the stability and longevity of transplanted cells.[41]

1.4 Infectious Disease Therapy

Cell therapy is emerging as a potential strategy for treating certain viral infections, although it is still in its early stages, and initial results are promising. This therapeutic approach mainly focuses on HSC transplantation (HSCT). The goal is to replace infected immune cells with healthy ones, potentially conferring resistance to the virus. Notably, the CCR5 Δ32/32 mutation, which provides resistance to HIV, has received significant attention in research. Studies have shown that patients receiving HSCT from donors carrying this mutation can achieve sustained viral remission.[42]

In addition, T-cell- and CAR-T–based therapies are emerging as promising strategies for HIV treatment. These approaches aim to enhance and direct the immune response to effectively target and eliminate HIV-infected cells. Early CAR-T designs targeted CD4, the primary receptor for HIV entry into T cells. However, these modified T cells remain susceptible to HIV infection.[43] Recent advances have led to the development of more sophisticated CAR constructs incorporating broadly neutralizing antibodies (bNAbs) that target multiple epitopes on the HIV envelope protein (gp120). These next-generation CAR-T cells aim to improve therapeutic efficacy by reducing viral escape and enhancing the clearance of infected cells.[44]

Advances in gene-editing technologies such as CRISPR/Cas9 now allow for the modification of HSCs to disrupt the HIV genome or increase resistance to infection. These approaches have shown promise in preclinical models and are currently under clinical evaluation. Multiple clinical trials are ongoing to assess the efficacy and safety of cell-based therapies for infectious diseases. For instance, trials using gene-modified T cells have demonstrated the ability to persist in the body and exert anti-HIV effects without significant adverse events.[45]

Chronic hepatitis B virus (HBV) infection poses a major public health concern due to its high prevalence and

potential progression to cirrhosis and hepatocellular carcinoma (HCC). Although current antiviral therapies suppress HBV replication, they rarely restore liver function.[46] Cell therapy, particularly using stem cells and adoptive T cells, has shown promising outcomes in HBV management. MSCs have demonstrated the ability to improve liver function and reduce mortality in patients with acute-on-chronic liver failure due to HBV (HBV-ACLF). Both bone marrow-derived MSCs (BM-MSCs) and umbilical cord-derived MSCs (UC-MSCs) can differentiate into hepatocyte-like cells, expressing liver-specific genes and functions such as albumin secretion and glycogen production.[47] Clinical trials have reported improved biochemical parameters, reduced incidence of severe infections and organ failure, and lower mortality in HBV-ACLF patients treated with MSCs compared to conventional therapies.[48] Phase II trials showed that allogeneic BM-MSC infusion improved liver function by modulating bilirubin levels, and UC-MSC therapy combined with plasma exchange also yielded favorable outcomes.[49,50]

Adoptive transfer of autologous T cells engineered to recognize specific antigens, such as CAR-T cells, enables recognition of HBsAg expressed on HBV-infected hepatocytes. The goal of adoptive T cell therapy is to restore T cell function impaired by HBV infection.[51] Current HBV antiviral therapies using nucleoside analogs (NAs) inhibit HBV-DNA synthesis but do not affect antigen production from HBV-RNA templates.[52] As a result, HBV-infected hepatocytes under NA treatment continue to express viral antigens similarly to untreated infected cells, making them targets for CAR- or TCR-T cells. Therefore, combining CAR/TCR-T therapy with NA treatment is proposed to enhance efficacy by limiting the formation of newly infected hepatocytes while targeting existing infected cells.[53]

1.5 Neurodegenerative Disease Therapy

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD) and Parkinson's disease (PD) are characterized by progressive deterioration of the structure and function of the nervous system, leading to significant cognitive and motor impairments.[54,55] Numerous studies are exploring the therapeutic potential of various stem cells, including MSCs, IPSCs, and NSCs. MSCs and IPSCs, in addition to their unique capacity to differentiate into neural cells, exert immunomodulatory effects that help repair damaged neural tissue and reduce neuroinflammation. The use of patient-derived IPSCs is increasingly favored due to reduced risk of immune rejection. Research is ongoing to evaluate their differentiation potential into various neural cell types, although concerns about tumorigenicity remain a significant challenge.[56]

Intravenous administration of MSCs allows these cells to migrate to injured regions and exert anti-inflammatory effects. Stem cell transplantation for AD primarily relies on their ability to differentiate into neurons and glial cells, replace damaged cells, release cytokines to activate endogenous neurogenesis, and modulate immune cell function. Transplanted stem cells can also differentiate into glial or progenitor cells to improve the supportive environment, ultimately restoring neural network function.[57] Another mechanism involves the secretion of exosomes, which reduce amyloid-beta (Aβ) plaque accumulation, a hallmark of AD pathology, and contribute to symptom alleviation. Transplanted stem cells also enhance synaptic plasticity and connectivity, which are often impaired in AD patients.[58]

PD is another debilitating neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra.[59] Dopaminergic drugs aim to maintain stable dopamine levels to alleviate symptoms, but do not halt disease progression and can cause significant side effects. Stem cells offer the potential to differentiate into dopaminergic neurons, replacing lost or damaged neurons in the substantia nigra and potentially restoring motor function.[60] ESCs are considered effective in this context, but ethical concerns remain a major limitation.[61] MSCs have also been shown to repair damaged dopaminergic neurons and improve symptoms such as rigidity and tremor. Clinical studies indicate that patients treated with MSCs, particularly in early disease stages, experience significant improvements. Patient-derived IPSCs enable the generation of autologous neurons, potentially reducing immune rejection and ethical concerns associated with ESCs. Phase I/II clinical trials have reported promising results in restoring motor function in PD patients.[62]

1.6 Infertility Therapy

Infertility is a major global concern, affecting approximately 15% of couples worldwide, and has profound psychological and social impacts, reducing quality of life. Male infertility is commonly associated with varicocele, undescended testes, testicular cancer, and azoospermia.[63] while female infertility is often linked to premature ovarian failure and uterine disorders. Advances in assisted reproductive technologies (ART) have significantly improved fertility outcomes, resolving nearly 80% of cases. However, a substantial proportion of couples remain infertile despite ART.

Recently, stem cells have been investigated as alternative treatments for infertility. Extensive research is being conducted on IPSCs and MSCs for their potential applications in azoospermia and premature ovarian failure. Most studies are currently in animal models, highlighting the need for further clinical trials to assess

efficacy in human populations.[64,65]

ESCs have shown high efficacy in treating infertility, but their use is limited by ethical concerns, whereas IPSCs overcome these issues and possess the potential to generate gametes.[66,67] MSCs derived from various sources, such as umbilical cord, placenta, adipose tissue, menstrual blood, and bone marrow, demonstrate strong regenerative capabilities in ovarian and endometrial function through anti-inflammatory, anti-apoptotic, and pro-angiogenic effects.[68]

The discovery of ovarian stem cells (OSCs) and identification of very small embryonic-like stem cells (VSELs) in adult reproductive tissues challenge the traditional view that the ovarian reserve is fixed at birth, suggesting that follicle regeneration continues throughout life. VSELs offer a promising autologous cell source with lower tumorigenic potential for infertility treatment. Spermatogonial stem cells (SSCs) are critical for male fertility, although challenges remain in their clinical application. Recent studies highlight the regulatory role of microRNAs (miRNAs) in stem cell differentiation, ovarian function restoration, and infertility therapy.[64]

1.7 Organ Replacement

In recent years, despite advances in transplantation technology, significant limitations remain, one of the most critical being the shortage of donors. Stem cells play a key role in organogenesis, which has garnered increasing attention (Figure 4). To generate tissues and organs, stem cells are cultured under three-dimensional (3D) conditions, and the resulting tissues, known as organoids, can be transplanted into living organisms. Organoids represent a promising tool for disease modeling, drug screening, and personalized medicine. Their application in organ regeneration and replacement therapies can reduce the need for full organ transplants and improve patients' quality of life.

Compared to conventional cell cultures, organoids better replicate the structural complexity, morphology, and biological interactions of real organs. Naturally, organoids undergo further maturation and development through interaction with the host body. Although organoid research is still in its early stages, preclinical evidence suggests that transplantation of organoids into the intestine, retina, kidney, liver, brain, heart, pancreas, and lungs is feasible and safe. Studies have demonstrated that transplanted organoids can differentiate into functional cells capable of interacting with host tissues. However, incomplete maturation and integration with host organs remain challenges for clinical application.[69]

Various techniques are being used to produce transplantable organs from stem cells, including 3D bioprinting and acellular scaffolds. 3D bioprinting is a powerful tool for reconstructing human tissues and organs, such as the heart, kidneys, and bones. In recent years, it has played a crucial role in addressing unresolved issues in transplantation, particularly the shortage of donor organs.[70] Another approach involves using natural acellular scaffolds, obtained by removing cells from native organs. These scaffolds retain the native biophysical and biochemical properties of the tissue while exhibiting low immunogenicity, creating a favorable environment for stem cell growth and differentiation.[71]

With the evolution of technologies and the establishment of ethical frameworks, the potential for stem cell–based organogenesis will continue to expand, offering a future where organ regeneration becomes a clinical reality.[72,73]

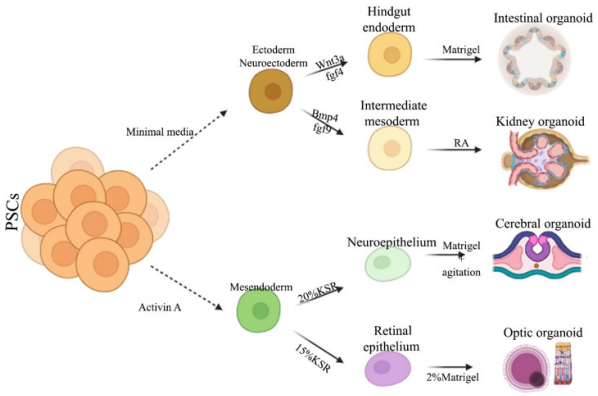

Figure 4 Differentiation potential of stem cells into various cell lineages and their assembly into complex organs using three-dimensional structures (The Figure is created with BioRender.com, accessed in May 2024)

2. Challenges in Cell Therapy

2.1 Large-Scale Cell Preparation

Producing cell therapy products on a large scale while maintaining their quality and functionality is a complex task. Ensuring sufficient cellular sources and adherence to Good Manufacturing Practice (GMP) standards is essential. Regulatory processes and stringent quality assessments are time-consuming and costly, representing major obstacles to large-scale production. Different countries have their own regulatory frameworks for cell therapy, leading to discrepancies in approval timelines and requirements, which can delay market access and patient availability. Regulatory authorities are encouraged to develop comprehensive international strategies that account for each target market and align overall development plans.[18]

Automation is considered a viable approach for achieving commercial-scale production. For example, in CAR-T cell manufacturing, there are currently two main automation approaches: fully automated closed systems and semi-automated systems. Fully automated systems

operate without any operator contact during production. Platforms such as CliniMACS Prodigy (Miltenyi Biotec) and Cocoon (Lonza) can isolate enriched T cells (CD3+, CD4+/CD8+) from an apheresis product and carry out culture and processing entirely within a closed system.[74,75] A major advantage of these systems is their compatibility with clean rooms requiring lower environmental control. However, final product vial filling still requires skilled operators in an ISO7 cleanroom. Fully automated systems may also face scalability limitations due to high infrastructure and cost requirements, and operators must have advanced troubleshooting skills to prevent production interruptions. An example includes robotic arms for isolating, expanding, harvesting, concentrating, and freezing adherent cells under cleanroom conditions, applied for human mesenchymal stromal cell production.[76]

2.2 Safety and Immunogenicity

Ensuring long-term safety is critical for regulatory approval of cell therapy products. Adverse effects such as immune reactions, tumorigenicity, or unwanted differentiation pose significant safety concerns.[77] Quality control (QC) is a crucial aspect of cell therapy development to ensure that cellular products meet required standards. Intrinsic biological variability, culture conditions, handling, and storage can significantly affect the final product, making QC criteria difficult to establish. Each production batch may exhibit variable characteristics, complicating product consistency. Comprehensive characterization of cells, including identity, differentiation potential, purity, and safety, is therefore essential.[12]

Allogeneic cell transplantation carries immunogenic risks, particularly graft-versus-host disease (GVHD) in hematopoietic stem cell (HSC) transplants. These risks are managed through immunosuppressive therapies and combinatorial approaches such as MSC co-transplantation. While immunosuppression increases infection risk, this can be mitigated by virus-specific T cell transfers. For example, donor-derived cytotoxic T lymphocytes (CTLs) targeting CMV have been investigated in a phase 4 trial (NCT03004261), where cells were primed ex vivo with CMV antigen peptides before infusion.

Genetically modified cells present additional immunogenic risks. Therapies involving receptor engineering may induce cross-reactivity, heighten immune responses, and alter cytokine signaling. CRS is a major CAR-T–associated adverse event, characterized by an excessive inflammatory cascade triggered by the infused cells and amplified by host immune cells such as macrophages. Untreated CRS can lead to shock, neurotoxicity, organ failure, and death.[78-80]

2.3 Efficacy Variability

The therapeutic effectiveness of cells after administration can vary significantly due to factors such as patient genetics, comorbidities, disease stage, treatment type and conditions, and the cellular source. Different cell types exert distinct mechanisms of action and efficacy. For instance, CAR-T cells are designed to target specific cancer cells, while MSC therapy may focus on tissue regeneration and immune modulation.

Cell preparation and quality strongly influence efficacy; well-cultured, viable cells tend to show better persistence and functional outcomes after transplantation.[81,82] The recipient's immune system also affects cell activity: immune responses may either reject transplanted cells or enhance their activity against diseases like cancer.[83,84] Other factors impacting cell performance include the local microenvironment, such as inflammation, hypoxia, and interactions with neighboring cells, which can support or hinder efficacy.[85,86]

Cell dose and timing are crucial for optimal therapeutic effect, highlighting the need for dose-optimization strategies.[87] Following ideal dosing, successful homing and migration of cells to the target tissue are critical. Poor homing results in low cell concentration at the target site and diminished treatment efficacy.[88,89] Migration and engraftment depend heavily on the delivery route; for example, intravenously administered T cells must sense chemokine gradients and endothelial markers to infiltrate solid tumors. Novel delivery routes for NK cells to brain tumors are under investigation for glioblastoma treatment (clinical trials: NCT03383978, NCT04489420).[80]

Post-transplantation monitoring and efficacy assessment allow protocol adjustments based on patient response.[90,91] Some cell therapies have long-lasting effects, whereas others require multiple administrations. Overall, cell therapy efficacy depends on complex interactions between biological factors, processing methods, and patient-specific conditions.[23,92]

2.4 Cellular Mechanisms of Action

The precise mechanisms by which cells exert therapeutic effects are often not fully understood. Examples include direct cell-to-cell interactions, cytokine and growth factor secretion, and immune modulation. Understanding these complex pathways is critical for optimizing therapies, but research in this area faces significant challenges.[93] Limited mechanistic knowledge hinders the development of more effective therapies and the identification of causes behind treatment failures.[94]

2.5 Cell Survival and Integrity

After administration, cell survival, integrity, and functional activity are essential for therapeutic success.

Factors influencing these include pH, oxygen levels, preparation and transport conditions, immune responses, nutrient availability, metabolic and physicochemical stress, and cellular aging. Strategies to enhance cell engraftment and longevity include ex vivo conditioning, combinatorial therapies, and genetic modification to improve survival, stability, and activity.[44]

Examples include preconditioning MSCs with cytokines or hypoxia to enhance their function, or combining NK cells with anti-tumor antibodies or checkpoint inhibitors to improve survival and activity (clinical trials: NCT02809092 for NK cells, NCT03958097).[80]

2.6 Cost and Accessibility

High costs of development, manufacturing, and clinical implementation limit patient access. Producing and preparing cells requires complex standardized processes, specialized facilities, advanced technologies, and high-quality materials, driving up total costs. Effective delivery often requires equipped hospitals and trained personnel, which may be unavailable in underserved areas. Personalized therapies, such as CAR-T, increase costs further due to patient-specific production.[95]

Automation advancements and the adoption of allogeneic therapies could reduce costs in the future.[80] Regulatory oversight and extensive testing also increase costs for providers and patients. Many insurance plans do not cover advanced cell therapies, limiting access for those unable to pay.[96] Additionally, long-term monitoring is necessary to ensure sustained outcomes, requiring continuous resources. Government funding, subsidies, and public investment can help lower costs, encourage competition, and expand insurance coverage to improve population-wide access.

2.7 Ethical Considerations

Cell therapy raises several ethical issues that require careful consideration. First, informed consent requires patients to be fully informed about the risks, benefits, and uncertainties associated with cell therapy. Second, the source of cells, particularly the use of ESCs, raises questions about the moral status of the embryo and potential human life. Third, donor rights must be protected, ensuring informed consent and avoiding exploitation in allogeneic therapies. Fourth, access and equity concerns could widen social disparities if only certain populations gain access. Fifth, commercialization and profit motives could conflict with patient welfare, highlighting the need to keep patient interest's primary. Sixth, long-term effects and unknowns raise concerns about unforeseen adverse events and the ethics of applying treatments without robust safety and efficacy data. Seventh, genetic manipulation issues involve unintended consequences, germline changes, and potential misuse, requiring stringent adherence to ethical guidelines, especially for vulnerable groups such as children or those unable to consent. Addressing these challenges requires ongoing dialogue among scientists, ethicists, policymakers, and the public to establish regulations and guidelines that prioritize patient welfare while promoting responsible innovation in cell therapy.[1,91,97]

2.8 Transport and Storage

Proper transportation and storage of cells in cell therapy is critical to maintaining viability, function, and safety. Key considerations include transportation where temperature control is essential because stem cells are typically stored in cryogenic conditions (~−196 °C in liquid nitrogen) while others may require refrigerated conditions (2–8 °C) with continuous temperature monitoring. Cryopreservation should use validated protocols with cryoprotectants (e.g., DMSO) to prevent ice crystal formation and osmotic stress during freezing and thawing. Packaging should involve insulated, shock-resistant containers to maintain temperature and protect cells from damage. Transit time should be minimized through efficient logistics. Documentation and compliance with proper labeling, traceability, and adherence to legal requirements (e.g., Good Distribution Practices) are essential. For storage, cryogenic storage in liquid nitrogen preserves cells long-term with continuous temperature monitoring and alarms to detect deviations. Apply controlled-rate freezing to minimize stress and ice crystal formation. Establish standardized storage protocols for freezing, monitoring, and regular assessment of stored cells. Implement standardized thawing protocols to maximize recovery and viability, including rapid controlled thawing followed by gentle handling in suitable media. Maintain inventory management with accurate records of cell types, quantities, and storage conditions. Perform regular QC checks to confirm viability and functionality after thawing. Adhere to these practices to ensure cell survival and functionality from collection to patient administration, thereby greatly improving the success of cell therapies.[80,98]

3. Future Prospects of Cell Therapy

Cell therapy represents significant advancements in medicine and disease treatment. While rapid technological and clinical progress continues, global cell therapy faces both immense potential and substantial challenges, from regulatory hurdles to equitable access.

With ongoing research in stem cell biology and differentiation, cell therapies are expected to become more effective. Gene-editing technologies like CRISPR-Cas9 enable precise modification of cell genomes, opening opportunities for engineered therapies with improved potency, safety, and targeting capabilities.

Integration with tissue engineering is expected to advance regenerative medicine, allowing for the development of complex and functional tissue replacements. Key challenges include scalable and cost-effective production of cell therapies. Advances in bioreactors, automation, and simplified production processes are expected to address these challenges.[99-101]

Additionally, artificial intelligence (AI) and machine learning were anticipated to play major roles in cell therapy by personalizing treatment plans, enabling rapid cell characterization and identification, improving data management, facilitating clinical trials and drug development, and enhancing post-treatment monitoring. These innovations are likely to reduce costs, accelerate therapeutic development, and improve clinical outcomes.[102]

4 Discussion

Cell therapy holds great promise for treating a wide range of diseases, from cancer and autoimmune disorders to degenerative conditions. Current applications focus on enhancing immune responses against tumors, repairing damaged tissues, and replacing lost cells. However, significant challenges remain, including the complexity and cost of producing cell-based products, the potential for immune rejection, and the need for precise targeting of therapeutic cells.

Looking forward, advances in cell therapy will depend on addressing these challenges through innovations in gene editing, biomaterials, and cell delivery technologies, ultimately enabling more effective, accessible, and personalized treatments. The integration of artificial intelligence (AI), tissue engineering, and gene editing is poised to revolutionize cell therapy by enabling precise, personalized, and scalable treatments. AI accelerates discovery and optimizes production by analyzing complex datasets and automating processes. Gene editing allows precise genetic modifications to improve cell function and safety. Tissue engineering creates supportive three-dimensional environments that enhance cell survival and integration.

Together, these technologies reduce costs and development timelines while improving the efficacy and safety of cell-based therapies, paving the way for more accessible, effective, and personalized treatments in the future.

Declarations

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Artificial Intelligence Disclosure
The authors confirm that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

Authors' Contributions
All authors actively participated in all stages of the study, including execution, analysis, and manuscript writing, and have reviewed and approved the final version of the manuscript.

Availability of Data and Materials
The data and materials used in this study are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare that they have no conflicts of interest related to the authorship or publication of this article.

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As this is a review study, no ethical approval was required.

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