Scholars LITERATURE

La Prensa Medica Argentina

Review Article

DOI: https://doi.org/10.47275/2953-4763-441
Volume 111 Issue 1

Stem Cell Therapies Overcoming Challenges and Shaping the Future of Disease Treatment

Sakshi Sukumaran Nair[1*], Vrinda Bharadwaj[2*], Chandrika Maddineni[3] and Aashish Raj T.Y.[4]

[1]Privolzhsky Research Medical University, Nizhny Novgorod, Russia
[2]Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India
[3]Kakatiya Medical College, Warangal, Telangana, India
[4]Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Abstract

Stem cell therapy has emerged as a transformative approach for treating a variety of human diseases, offering the potential to regenerate damaged tissues, restore lost functions, and address the underlying causes of chronic conditions. From neurodegenerative diseases like Parkinson's and Alzheimer's, to cardiovascular, autoimmune, and metabolic disorders, stem cells such as induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) have demonstrated therapeutic promise in preclinical and clinical trials. These therapies provide not only symptomatic relief but also the possibility of functional recovery, improving patient quality of life and reducing long-term healthcare costs. While these therapies offer groundbreaking solutions for previously untreatable ailments, challenges including immune rejection, ethical concerns, scalability, and long-term safety remain. The risk of tumorigenesis and the difficulty in ensuring the integration of transplanted cells into host tissues are ongoing issues. Ongoing research and technological innovations, including gene editing, advanced biomaterials, and personalized medicine, are key to overcoming these barriers. As these obstacles are addressed, stem cell therapy has the potential to significantly improve patient outcomes, revolutionize medical treatments, and advance human welfare on a global scale, offering hope for millions of individuals with chronic and debilitating diseases.

Keywords: Stem cells, Pluripotent cells, Regenerative medicine, Therapeutic applications, Clinical trials

Correspondence to: Sakshi Sukumaran Nair and Vrinda Bharadwaj, Privolzhsky Research Medical University, Nizhny Novgorod, Russia and Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

Citation: Nair SS, Bharadwaj V, Maddineni C, Raj TYA (2025) Stem Cell Therapies Overcoming Challenges and Shaping the Future of Disease Treatment. Prensa Med Argent, Volume 111:1. 441. DOI: https://doi.org/10.47275/2953-4763-441

Received: December 03, 2024; **Accepted:** February 18, 2025; **Published:** February 24, 2025

Introduction

Stem cells, the fundamental building blocks of life, have long captivated the scientific community for their unique ability to self-renew and differentiate into various specialized cell types [1]. These undifferentiated cells exist in both embryonic and adult tissues, playing critical roles in development, repair, and maintenance of the body [1]. The discovery of stem cells in the early 20th century emerged from pioneering research in hematology, where scientists observed the regenerative capabilities of blood-forming cells (Figure 1) [2]. This was followed by the landmark identification of mouse embryonic stem cells (ESCs) in 1981, and later human ESCs in 1998, setting the stage for transformative scientific and medical breakthroughs [3]. Early studies focused on understanding their intrinsic properties and potential for generating specific cell types *in vitro*, laying the groundwork for regenerative medicine and disease modeling [4].

Advances in molecular biology and genetics have significantly deepened our understanding of stem cells. Researchers unraveled the signaling pathways and transcriptional networks that govern their pluripotency and differentiation. Notably, the introduction of iPSCs by Shinya Yamanaka in 2006 marked a paradigm shift, as it became possible to reprogram adult somatic cells back into a pluripotent state [5]. This revolutionary technique bypassed ethical concerns associated with ESCs and opened new avenues for personalized medicine. Furthermore, breakthroughs in single-cell technologies have provided unprecedented insights into the heterogeneity and dynamic nature of stem cell populations, revealing how intrinsic and extrinsic factors influence their behavior across different tissue environments [6, 7].

Today, stem cells are at the forefront of translational research, driving innovations in regenerative therapies, drug discovery, and disease modeling. For example, stem cell-based treatments for conditions such as macular degeneration, spinal cord injuries (SCI), and type 1 diabetes (T1D) have shown promising results in clinical trials [8]. Organoids, three-dimensional (3D) cellular structures derived from stem cells, have revolutionized *in vitro* modeling of human organs, offering valuable platforms for studying diseases like cancer and rare genetic disorders [9, 10]. Despite these advancements, challenges such as immune rejection, genetic instability, and scalability continue to impede the widespread application of stem cell therapies in clinical practice [11].

The future of stem cell science promises to transcend current limitations through interdisciplinary approaches integrating

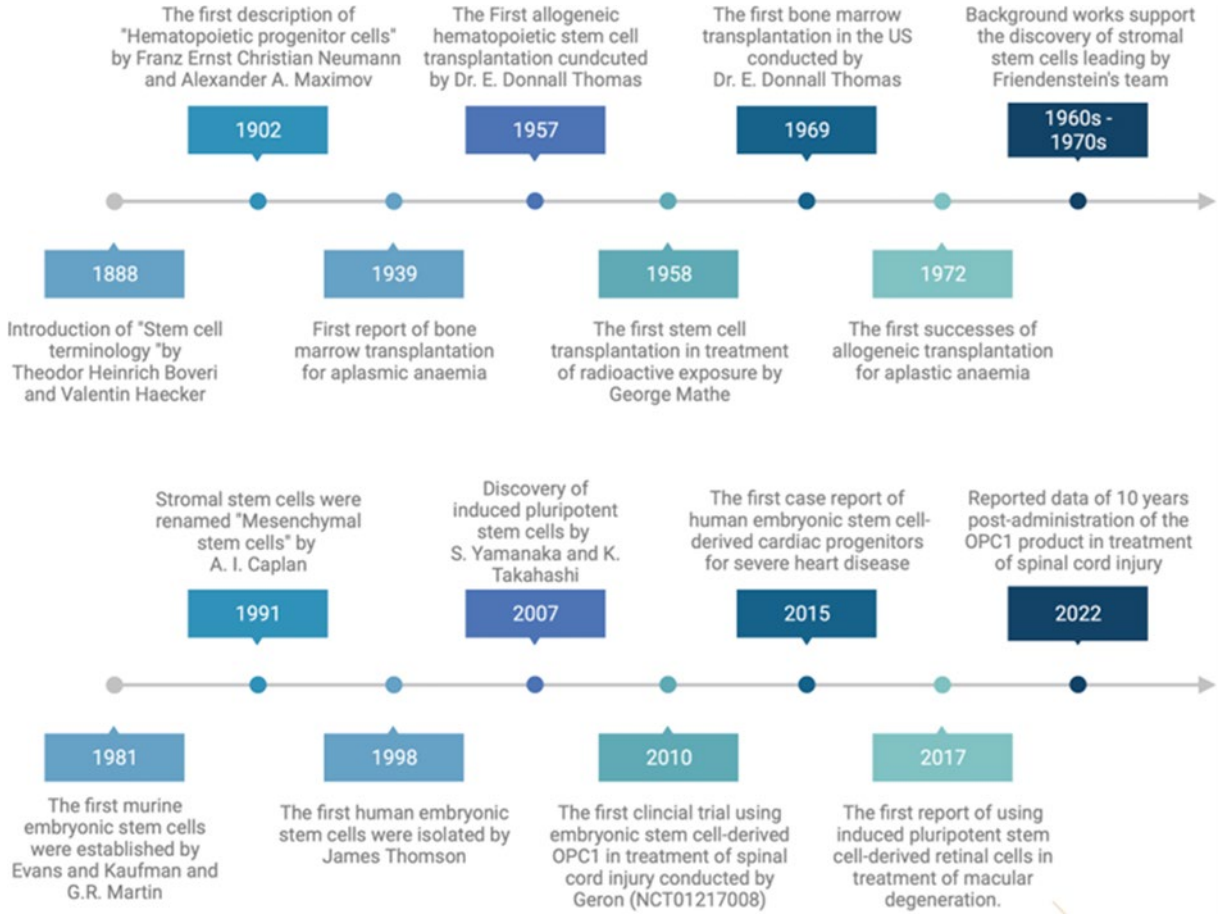

Figure 1: The timeline of major discoveries and advances in basic research and clinical applications of stem cell-based therapy. Reproduced from [3].

bioengineering, artificial intelligence, and synthetic biology [12]. Scientists are exploring strategies to enhance stem cell potency, refine differentiation protocols, and develop universal donor cells to minimize immune rejection. Moreover, the advent of CRISPR-Cas9 and other gene-editing technologies has enabled precise genetic modifications, allowing for the correction of disease-causing mutations in patient-derived stem cells [13]. As the field progresses, there is growing interest in understanding the aging process of stem cells and leveraging this knowledge to combat age-related degenerative diseases.

While stem cells hold immense potential for transforming medicine, their use also raises important ethical, regulatory, and societal questions [14]. Issues such as equitable access, long-term safety, and the possibility of misuse in areas like human enhancement demand careful consideration. As we stand on the brink of a new era in biomedical science, the challenge lies not only in advancing the technical and biological aspects of stem cell research but also in fostering responsible innovation that aligns with societal values and needs. With sustained investment in research and a commitment to ethical principles, stem cells are poised to reshape the future of medicine and human health in ways that were once considered the realm of science fiction.

Stem Cells: Etiology and Hierarchy

Stem cells are the foundational cells of the body, characterized by their ability to self-renew and differentiate into various specialized cell types [15]. Their etiology traces back to the earliest stages of embryonic development. During fertilization, the zygote forms and undergoes rapid cell division to produce the blastocyst, a hollow structure containing the inner cell mass. The inner cell mass is the origin of ESCs, which are pluripotent, meaning they can give rise to almost all cell types of the body. In adults, stem cells are present in specialized niches, where they function as a repair system to maintain tissue integrity. For example, hematopoietic stem cells (HSCs) reside in the bone marrow and produce all types of blood cells, while MSCs in the stroma contribute to bone, cartilage, and fat formation [16].

Stem cells can be classified hierarchically based on their potency, which reflects their differentiation potential (Figure 2 and Table 1). At the top of this hierarchy are totipotent cells, such as the zygote and its early cleavage-stage descendants, which can form both embryonic and extra-embryonic tissues like the placenta. Below these are pluripotent cells, such as ESCs and iPSCs, which can generate cells from all three germ layers-ectoderm, mesoderm, and endoderm-but cannot form extra-embryonic tissues [17]. For instance, ESCs from mice have been used to create entire mouse embryos in the laboratory, highlighting their developmental capabilities. At the next level are multipotent stem cells, which are restricted to specific lineages, such as HSCs generating blood cells or neural stem cells (NSCs) forming neurons, astrocytes, and oligodendrocytes (Table 2) [18].

Beneath multipotent cells in the hierarchy are oligopotent and unipotent stem cells. Oligopotent stem cells can differentiate into a limited subset of cell types within a particular lineage. For example, myeloid progenitor cells give rise to granulocytes and macrophages,

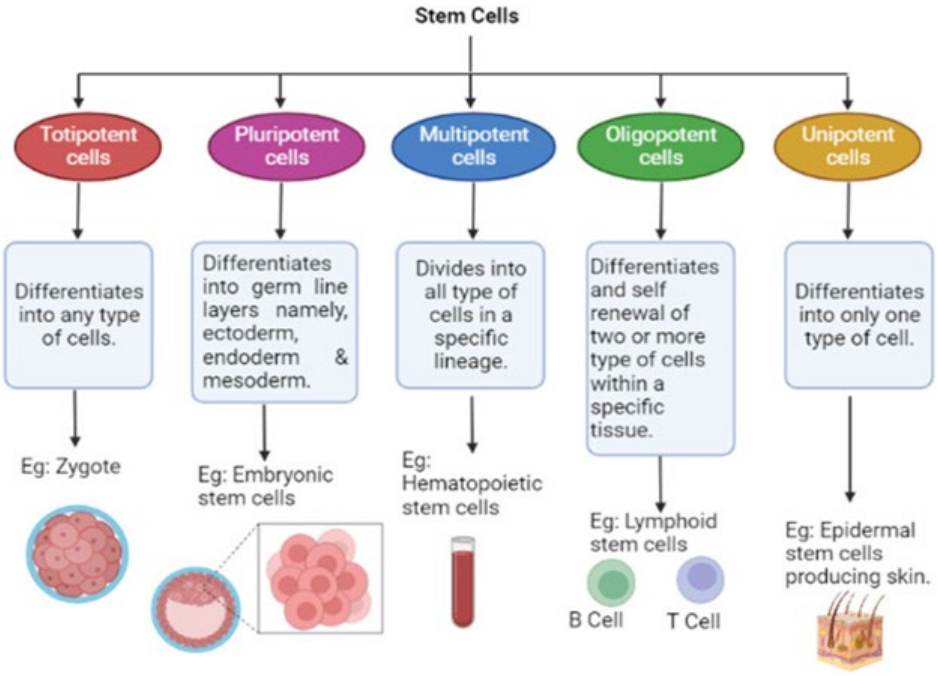

Figure 2: Stem cell types and properties. Reproduced from [16].

Table 1: Stem cells etiology and hierarchy.

Category	Description	Examples	Properties	Limitations
Totipotent stem cells	Stem cells that can differentiate into all cell types, including extra-embryonic tissues (e.g., placenta). These cells are present only during early stages of embryonic development.	Zygote (fertilized egg)	Can generate any cell type, including extra-embryonic tissues. Full developmental potential.	Only present in early embryonic development, not available for therapeutic use.
PSCs	Cells that can differentiate into any cell type of body, but not extra-embryonic tissues.	ESCs and iPSCs	Can differentiate into all cell types of the body. Can be derived from somatic cells (iPSCs).	Ethical issues surrounding ESC use. Potential for tumor formation. Risk of immune rejection (allogeneic ESCs).
Multipotent stem cells	Stem cells that are more restricted in differentiation and can give rise to a limited range of cell types, typically related to the tissue in which they reside.	HSCs and MSCs	Can generate a limited range of cells within a specific tissue. Less risk of tumor formation compared to PSCs.	Limited to certain cell types. Less regenerative capacity compared to pluripotent cells.
Oligopotent stem cells	Cells that can differentiate into a few closely related cell types.	NSCs (can generate different types of neural cells)	More restricted differentiation potential. Can self-renew.	Restricted to a smaller number of cell types. Limited ability to regenerate large-scale tissue.
Unipotent stem cells	Stem cells that can only differentiate into one cell type, but they have the ability to self-renew.	Spermatogonial stem cells (only generate sperm cells)	Self-renewal capacity. Can produce only one cell type.	Very limited differentiation potential. Limited application in regenerative medicine.

while lymphoid progenitors produce T cells, B cells, and natural killer cells [19]. Unipotent stem cells, on the other hand, are restricted to producing a single cell type. A classic example is epidermal stem cells, which exclusively generate keratinocytes to replenish the skin's outer layer [20]. Despite their limited differentiation capacity, unipotent stem cells retain the ability to self-renew, ensuring the maintenance of specific tissues over time [21].

The concept of the stem cell hierarchy is not rigid and may vary depending on the tissue and its requirements [22]. For instance, the intestinal epithelium is maintained by multipotent intestinal stem cells located in the crypts of Lieberkühn [23]. These cells continuously divide into absorptive and secretory cells, which migrate upwards to replace damaged or sloughed-off intestinal lining. Similarly, satellite cells in skeletal muscle act as adult stem cells capable of generating myoblasts for muscle repair following injury [24]. These examples illustrate how the stem cell hierarchy operates dynamically to meet the specific needs of different tissues.

Recent advances have blurred the boundaries of the stem cell hierarchy by enabling cellular reprogramming and trans differentiation [25]. Yamanaka factors, for example, can reprogram differentiated somatic cells into pluripotent iPSCs, effectively "resetting" their position in the hierarchy [26]. Similarly, direct conversion of one cell type into another, such as fibroblasts into neurons, has demonstrated the plasticity of cellular identities [27]. These innovations have expanded our understanding of lineage potential and challenged the traditional view of a unidirectional differentiation hierarchy, with implications for regenerative medicine and disease modeling.

The study of stem cell etiology and hierarchy not only illuminates

Table 2: Stem cells, their properties, role, source, origin, and mechanism of action.

Stem cell type	Properties	Role	Source	Origin	Mechanism of action
ESCs	Pluripotent (can differentiate into any cell type). High proliferative capacity.	Tissue regeneration. Disease modeling. Research applications.	Blastocyst-stage embryos.	Derived from early-stage embryos (blastocyst).	ESCs differentiate into various cell types through signaling pathways such as Wnt, notch, and BMP signaling, depending on the environmental cues and culture conditions. Their pluripotency is regulated by transcription factors like Oct4 and Sox2.
IPSCs	Pluripotent. Genetically reprogrammed from somatic cells. Avoids ethical concerns associated with ESCs.	Disease modeling. Regenerative medicine. Patient-specific therapies.	Adult somatic cells (e.g., fibroblasts, skin cells).	Derived from differentiated adult cells reprogrammed back to pluripotent state.	Reprogramming of somatic cells is induced by the expression of specific transcription factors (e.g., Oct4, Sox2, Klf4, c-Myc) that reset the epigenetic landscape to a pluripotent state.
MSCs	Multipotent (can differentiate into bone, cartilage, fat, and muscle). Immune-modulatory properties.	Regenerative medicine. Wound healing. Cartilage and bone repair.	Bone marrow, adipose tissue, umbilical cord, dental pulp.	Derived from mesodermal tissue (connective tissue).	MSCs secrete growth factors and cytokines that modulate immune responses, promote tissue repair, and can differentiate into mesodermal lineages (bone, cartilage, muscle). They act through paracrine signaling and immune modulation.
HSCs	Multipotent (produce blood cells). Long-term self-renewal capability.	Blood regeneration. Treatment of blood disorders (e.g., leukemia).	Bone marrow, peripheral blood, umbilical cord blood.	Derived from hematopoietic tissues (bone marrow).	HSCs differentiate into all types of blood cells (red blood cells, white blood cells, platelets) through hierarchical differentiation, with self-renewing divisions ensuring constant replenishment of the blood system.
NSCs	Multipotent (can differentiate into neurons, astrocytes, and oligodendrocytes). Neurogenic capacity.	Neural regeneration. Brain and spinal cord repair.	Brain (e.g., hippocampus), spinal cord, retina.	Derived from ectodermal tissue (nervous system).	NSCs differentiate into neurons and glial cells through signaling pathways such as notch and Wnt. They are crucial for neurogenesis during development and hold potential for repairing damaged neural tissue in neurodegenerative diseases.
Epithelial stem cells	Multipotent (differentiate into various epithelial cell types). Essential for tissue homeostasis.	Skin regeneration. Wound healing. Tissue repair.	Skin, cornea, respiratory epithelium.	Derived from ectodermal tissue (epithelial layer).	Epithelial stem cells are responsible for the regeneration of epithelial tissues. They undergo asymmetric division to maintain the stem cell pool while producing differentiated cells for tissue renewal and repair.
Endothelial stem cells	Multipotent (can differentiate into endothelial cells). Regenerative capacity for blood vessels.	Vascular regeneration. Wound healing. Angiogenesis.	Bone marrow, adipose tissue, peripheral blood.	Derived from mesodermal tissue (vascular endothelium).	Endothelial stem cells contribute to angiogenesis by differentiating into endothelial cells, forming new blood vessels, and secreting factors that promote tissue repair and vascularization.
Germline stem cells	Self-renewing. Potential to differentiate into germ cells (sperm and eggs).	Reproductive cell regeneration. Fertility treatments.	Testes (male), ovaries (female).	Derived from germline tissue.	Germline stem cells divide asymmetrically to maintain a stem cell pool while differentiating into germ cells. They are crucial for reproduction and could be used in fertility treatments.
Cardiac stem cells	Multipotent (can differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells).	Cardiac regeneration. Repairing heart tissue after injury.	Heart (e.g., atrial and ventricular regions).	Derived from mesodermal tissue (cardiac lineage).	Cardiac stem cells promote tissue repair by differentiating into heart muscle cells (cardiomyocytes) and endothelial cells. They also secrete paracrine factors that support regeneration after myocardial infarction or heart failure.

fundamental aspects of biology but also provides a framework for therapeutic interventions [28]. For example, HSCs transplantation has been used for decades to treat blood cancers like leukemia, leveraging the hierarchical differentiation of these cells to restore hematopoietic function [29]. The ongoing exploration of stem cell behavior in various contexts, from development to aging and disease, continues to refine our understanding of how stem cells maintain tissue homeostasis, repair damage, and contribute to organismal health [30, 31]. This knowledge underpins the promise of stem cell therapies in addressing a range of medical challenges, from organ failure to genetic disorders.

Stem Cells Based Therapies in Human Diseases

Stem cell-based therapies are increasingly becoming a cornerstone of regenerative medicine, addressing human diseases through innovative treatments that aim to restore, replace, or regenerate damaged tissues (Table 3) [32]. At the forefront of this progress are HSC transplants, which have been widely used for decades to treat blood-related disorders such as leukemia, lymphoma, and sickle cell anemia [33]. These transplants involve the infusion of healthy donors or autologous HSCs into patients to regenerate functional blood and immune systems. Advances in HSC mobilization, cryopreservation, and genetic modification, such as CRISPR-based correction of genetic mutations, have further refined these therapies, expanded their applicability and improved outcomes [34]. MSCs offer numerous benefits and opportunities (Figure 3).

In recent years, MSCs have gained attention for their therapeutic potential due to their immunomodulatory and anti-inflammatory properties [36]. MSCs, derived from bone marrow, adipose tissue, or umbilical cord, are being investigated in clinical trials for conditions such as graft-versus-host disease (GVHD), osteoarthritis, and chronic inflammatory diseases [37,38]. For example, MSCs have shown promise in mitigating GVHD by suppressing excessive immune responses following bone marrow transplantation [39]. Additionally, MSC-based products are being developed for cartilage repair in degenerative joint diseases, with some therapies already receiving conditional approval in certain regions, such as Japan's expedited regulatory pathways [40].

The use of PSCs, including ESCs and iPSCs, has enabled the development of more sophisticated therapeutic strategies for complex diseases. One notable example is the treatment of retinal disorders such as age-related macular degeneration. Clinical trials using retinal pigment epithelial (RPE) cells derived from ESCs or iPSCs have shown encouraging results in halting vision loss and even partially restoring sight in patients [41]. Similarly, researchers are exploring iPSC-derived dopaminergic neurons to treat Parkinson's disease, aiming to replace the degenerated neurons responsible for motor symptoms [42]. These

Table 3: Stem cell-based therapies, therapeutic outcomes, and challenges.

Disease	Stem cell type	Therapeutic outcomes	Challenges
Parkinson's disease	ESCs and iPSCs	Potential to replace lost dopaminergic neurons. Improved motor function in preclinical models and early clinical trials.	Risk of tumor formation. Difficulty in ensuring long-term cell survival and integration with brain tissue.
Cardiovascular disease (e.g., myocardial infarction)	MSCs and iPSCs	Improved heart function. Reduced scar tissue. Enhanced tissue regeneration in clinical trials.	Poor engraftment and integration with heart tissue. Risk of arrhythmias. Immunogenicity in allogeneic cells.
T1D	MSCs and iPSCs	Restoration of insulin-producing cells. Improved blood glucose control.	Immune rejection of transplanted cells. Difficulty in generating functional, insulin-secreting beta cells.
Spinal cord injury	NSCs and MSCs	Partial restoration of motor function. Promotion of nerve regeneration in preclinical studies and early clinical trials.	Limited axon regeneration. Difficulty in creating long-lasting functional recovery.
Osteoarthritis	MSCs	Reduced pain and inflammation. Enhanced cartilage regeneration. Improved joint function in clinical trials.	Limited tissue integration. Variability in patient response. Difficulty in large-scale cartilage regeneration.
Macular degeneration	RPE cells derived from iPSCs	Improved vision stabilization. Partial restoration of retinal function in clinical trials.	Long-term survival of transplanted cells. Risk of immune rejection. Technical difficulty in cell integration.
Leukemia and other blood disorders	HSCs	Restoration of healthy blood cells. Effective bone marrow transplantation to treat leukemia and lymphoma.	Risk of GVHD. Need for immunosuppressive therapy in allogeneic transplants.
Muscle degeneration (e.g., Duchenne muscular dystrophy)	Muscle stem cells (e.g., satellite cells)	Muscle regeneration. Improved muscle strength and function in preclinical models.	Limited engraftment in muscle tissue. Difficulty in achieving large-scale tissue regeneration.
Liver diseases (e.g., cirrhosis and acute liver failure)	Hepatic stem cells and MSCs	Improved liver function. Reduced need for liver transplantation. Liver tissue regeneration in clinical trials.	Low efficiency of engraftment. Risk of tumor formation. Immune rejection.
Autoimmune diseases (e.g., multiple sclerosis, and rheumatoid arthritis)	MSCs	Reduced inflammation. Immunomodulation. Improved disease markers and patient function in clinical trials.	Variability in patient responses. Immune rejection risks. Long-term safety concerns.
Wound healing (Chronic ulcers, burns)	MSCs and fibroblasts	Accelerated tissue regeneration. Enhanced wound closure. Reduced scarring and inflammation.	Risk of fibrosis. Difficulty in controlling the differentiation of stem cells into the desired tissue type.
Neurological disorders (e.g., stroke and amyotrophic lateral sclerosis (ALS))	NSCs and MSCs	Restoration of neuronal function. Neuroprotection and tissue repair in stroke and ALS models.	Limited neuronal regeneration. Difficulty in achieving functional recovery. Immune rejection in some cases.
Organ transplantation (e.g., kidney, liver, and heart)	MSCs and HSCs	Prevention of organ rejection. Enhanced engraftment and tissue repair. Reduced need for immunosuppressive therapy.	Difficulty in large-scale production. Long-term efficacy and safety concerns. Risk of immune rejection.

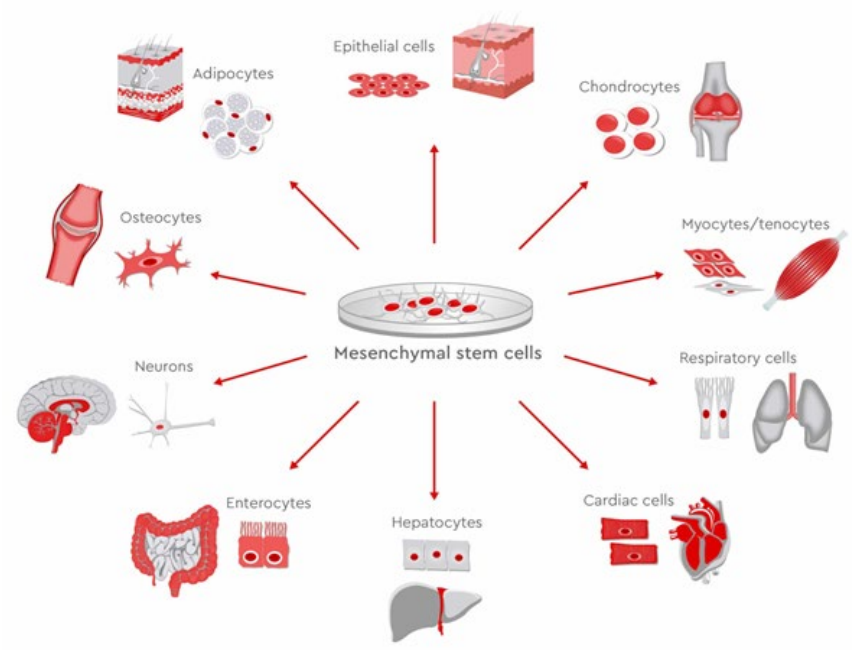

Figure 3: Multipotent nature of MSCs in regenerative medicine. Reproduced from [35].

advancements highlight the ability of PSCs to generate specialized cells for targeted therapeutic interventions.

Organoids, 3D miniaturized versions of organs derived from stem cells, represent another cutting-edge application of stem cell-based therapies. While still in experimental stages, organoids are being utilized to model diseases, test drugs, and explore the feasibility of organ regeneration. For instance, liver organoids are being developed to treat liver failure, while pancreatic organoids hold potential for managing diabetes by replacing insulin-producing beta cells [43]. In 2021, scientists successfully transplanted lab-grown organoids into animals, demonstrating the possibility of integrating these constructs into functional tissue networks, a crucial step toward clinical translation in humans [44].

Despite these advancements, significant challenges remain in the clinical application of stem cell-based therapies. Issues such as immune rejection, tumorigenicity, scalability, and high costs continue to hinder widespread adoption [45, 46]. Nonetheless, innovative approaches are emerging to overcome these obstacles. Universal donor stem cells, engineered to evade immune detection, are being developed to reduce the need for immunosuppression [47]. Meanwhile, bioprinting and scaffold-based technologies are improving the scalability and structural integration of stem cell-derived tissues [48]. As the field advances, stem cell-based therapies are poised to revolutionize medicine by offering curative treatments for previously untreatable diseases, from neurodegenerative disorders to organ failure.

Therapeutic Translation of Stem Cell Research

HSC therapy: Proven success in blood disorders

HSCs are among the most well-established tools in regenerative medicine, primarily used to treat hematological malignancies and blood disorders [49]. The transplantation of HSCs, often referred to as bone marrow transplantation, has been a standard of care for decades for conditions such as leukemia, lymphoma, and aplastic anemia [50]. By replenishing the blood-forming system, HSC therapy allows for the eradication of diseased cells, followed by the regeneration of healthy blood and immune cells. Advances in matching donor-recipient compatibility and improved conditioning regimens have significantly enhanced survival rates and reduced complications like GVHD [51].

Recent developments have focused on genetically modifying HSCs to address genetic disorders such as sickle cell anemia and beta-thalassemia [52]. Using CRISPR-Cas9 or other gene-editing technologies, researchers have corrected disease-causing mutations in patient-derived HSCs [53]. For instance, trials led by CRISPR Therapeutics and Vertex Pharmaceuticals have shown promising results in treating these conditions by engineering HSCs to produce functional hemoglobin [54, 55]. These advancements highlight the potential for HSCs to go beyond traditional transplantation and offer curative solutions for inherited blood disorders.

MSCs: For immune modulation and tissue repair

MSCs have emerged as a versatile tool in the treatment of inflammatory and degenerative diseases, owing to their immunomodulatory and regenerative properties [56]. MSCs can secrete bioactive molecules that suppress inflammation and promote tissue repair, making them suitable candidates for conditions such as osteoarthritis, GVHD, and Crohn's disease [57]. For example, MSCs have been approved in some regions for treating severe GVHD in children, providing a viable alternative to conventional therapies that fail to manage the condition effectively [58].

In degenerative joint diseases, MSC-based products like "stem cell injections" are being explored for cartilage regeneration. In clinical trials, MSCs have demonstrated the ability to reduce pain and improve joint function in osteoarthritis patients [40]. Moreover, researchers are investigating their role in cardiovascular diseases by using MSCs to repair damaged heart tissue following myocardial infarction [59]. These therapeutic applications exemplify the broad potential of MSCs across a range of medical conditions.

PSCs: For regenerative therapies

PSCs, including ESCs and iPSCs, have enabled new frontiers in regenerative medicine due to their ability to differentiate into any cell type [60]. These cells are particularly promising for treating diseases where cell replacement is critical, such as neurodegenerative disorders and retinal diseases. For example, clinical trials using RPE cells derived from ESCs or iPSCs have demonstrated significant potential in halting or reversing vision loss in patients with age-related macular degeneration [61].

PSCs are also being used to address Parkinson's disease, where dopaminergic neurons derived from iPSCs are transplanted into patients to replace lost neurons [62]. Preliminary results from these trials indicate improved motor symptoms, showcasing the viability of this approach. As iPSCs can be derived from a patient's own cells, they circumvent the ethical concerns associated with ESCs and reduce the risk of immune rejection, making them a cornerstone of personalized medicine [63].

Organoids: As tools for disease modeling and therapeutics

Stem cell-derived organoids, miniature 3D structures mimicking human organs, are transforming the landscape of disease modeling and therapeutic research [64]. Organoids provide an unparalleled platform to study the pathophysiology of complex diseases and test potential treatments *in vitro*. For instance, brain organoids have been used to model neurological disorders such as Alzheimer's disease and autism, while liver organoids are being employed to study drug toxicity and liver regeneration [65, 66].

Therapeutically, organoids hold promises for replacing damaged or failing tissues. For example, pancreatic organoids derived from stem cells are being explored as a potential treatment for T1D by generating insulin-producing beta cells [67]. Liver organoids, on the other hand, could offer a solution for patients with end-stage liver disease, reducing dependence on donor organs [68]. While clinical translation remains challenging, the integration of organoid technology with bioengineering and transplantation research is rapidly advancing.

Stem cell-based gene therapy for inherited disorders

Gene therapy using stem cells is revolutionizing the treatment of genetic diseases by enabling precise correction of underlying mutations [69]. In this approach, patient-derived stem cells are genetically modified to repair the faulty gene and subsequently transplanted back into the patient. For example, lentiviral-mediated gene therapy for adrenoleukodystrophy, a severe neurodegenerative disorder, has demonstrated significant success in clinical trials by restoring functional proteins in HSCs [70, 71].

Similarly, iPSCs are being employed to develop personalized therapies for rare genetic diseases like spinal muscular atrophy [72].

By reprogramming a patient's cells into iPSCs, researchers can study the disease *in vitro*, identify potential treatments, and even correct the mutation before differentiating the iPSCs into functional cell types for transplantation [73]. These examples illustrate how the combination of stem cell technology and gene editing is paving the way for curative therapies for previously untreatable conditions.

From infarction to function: Stem cells transforming cardiology

Stem cell research in cardiology has shown significant potential for addressing heart diseases, particularly those caused by myocardial infarction and heart failure, where cardiomyocytes are lost due to ischemic injury [74]. Since the adult heart has limited regenerative capacity, stem cell-based approaches aim to repair or replace damaged heart tissue. Early studies focused on using MSCs and bone marrow-derived stem cells (BMSCs) due to their regenerative and paracrine signaling capabilities [75]. These cells release growth factors and cytokines that promote angiogenesis, reduce inflammation, and improve cardiac function. For example, clinical trials such as the REPAIR-AMI (Randomized Evaluation of Stem Cell Therapy for Acute Myocardial Infarction) trial demonstrated that BMSCs injected into the myocardium improved left ventricular ejection fraction in patients' post- myocardial infarction [76].

Recent advancements have shifted the focus toward PSCs, including ESCs and iPSCs, due to their ability to differentiate into cardiomyocytes [77]. IPSC-derived cardiomyocytes have shown promise in preclinical models, where they integrate into host heart tissue, restore contractile function, and improve overall cardiac performance [74]. One notable example is the use of iPSC-derived cardiac patches, which are engineered tissue constructs containing cardiomyocytes and vascular cells. Studies have shown that these patches can be transplanted into infarcted areas of the heart to enhance myocardial repair [78]. In Japan, a pioneering clinical study transplanted a sheet of iPSC-derived cardiomyocytes into a heart failure patient, marking a significant step toward therapeutic applications [79].

Challenges remain in translating these therapies to routine clinical use, including ensuring long-term engraftment, avoiding arrhythmias, and addressing immune rejection. Bioengineering approaches, such as 3D bioprinting and the use of biodegradable scaffolds, are being combined with stem cells to improve the structural integration and functional recovery of heart tissue [80]. Furthermore, research into gene editing, such as CRISPR-Cas9, is exploring ways to enhance the survival and functionality of stem cell-derived cardiomyocytes in harsh ischemic environments [81]. As these technologies advance, stem cell-based therapies hold immense promises for revolutionizing the treatment of cardiovascular diseases, potentially providing curative solutions for conditions that were previously considered irreversible.

Closing the gap: Bioengineered scaffolds and stem cells in wound care

Stem cell research in regeneration and wound healing has provided transformative insights into enhancing tissue repair and promoting recovery in acute and chronic injuries [82]. Adult stem cells, such as MSCs, are a cornerstone of this field due to their regenerative and immunomodulatory capabilities. MSCs, derived from sources such as bone marrow, adipose tissue, and umbilical cord, promote wound healing through paracrine signaling, secretion of growth factors, and differentiation into tissue-specific cells [83]. A key example is their use in chronic non-healing wounds like diabetic foot ulcers. In a study by Dash et al. [84], MSC-derived exosomes were found to accelerate wound healing by enhancing angiogenesis and epithelialization, offering a non-invasive alternative to direct cell transplantation.

PSCs, for example iPSCs, have further expanded the therapeutic landscape for regeneration and wound healing. iPSCs can differentiate into skin-specific cell types, such as keratinocytes and fibroblasts, enabling their use in skin grafting and tissue engineering [85]. For instance, iPSC-derived keratinocytes integrated seamlessly into damaged skin, promoting regeneration without significant immune rejection [86]. Additionally, iPSCs have been used to create bioengineered skin equivalents, which can be applied to large burn injuries or deep tissue wounds. These constructs mimic the natural architecture of human skin and provide a functional and aesthetic restoration in preclinical and early clinical trials [87].

Stem cell-based therapies are also being explored for more complex wound healing scenarios, such as tissue regeneration after severe burns or traumatic injuries. In these cases, bioengineered scaffolds seeded with stem cells play a crucial role in providing structural support and guiding cell proliferation and differentiation [88]. For example, MSCs embedded in collagen scaffolds to treat deep dermal burns in animal models. The approach led to reduced scarring, faster re-epithelialization, and improved tensile strength of regenerated skin [89]. These findings highlight the synergistic potential of combining stem cell therapy with advanced biomaterials to optimize regenerative outcomes.

Despite the progress, significant challenges remain in translating stem cell-based wound healing therapies to widespread clinical use. Issues such as cell survival, scalability, and regulatory hurdles need to be addressed [90]. Moreover, the potential for tumorigenesis, particularly with PSCs, requires stringent quality control measures. Current research is addressing these challenges by focusing on cell-free therapies, such as the use of MSC-derived exosomes and secretomes, which retain the therapeutic effects of stem cells without the associated risks [91]. With ongoing advancements in stem cell biology and tissue engineering, stem cell-based approaches to regeneration and wound healing are poised to redefine standards of care for a wide range of injuries and chronic conditions.

Regenerating the brain: Stem cell innovations in neurological disorders

Stem cell research has opened groundbreaking avenues for treating neurological disorders, many of which involve irreversible damage to the central nervous system (CNS). MSCs and NSCs have been extensively studied for their neuroprotective and regenerative effects [92]. MSCs, in particular, exhibit potent paracrine signaling, secreting neurotrophic factors that reduce inflammation and promote neural repair [93]. In a clinical trial, MSCs demonstrated promising outcomes in multiple sclerosis patients, significantly reducing immune-mediated demyelination and supporting remyelination of damaged neurons. These findings underscore the potential of MSC-based therapies to modulate neuroinflammation in autoimmune neurological conditions [94].

IPSCs have revolutionized the field of neurology by enabling the generation of patient-specific neurons, glia, and other CNS cell types [95]. This approach offers personalized regenerative solutions for diseases like Parkinson's disease, where dopaminergic neurons are progressively lost. Clinical trials led by Takahashi et al. [96], transplanted iPSC-derived dopaminergic progenitor cells into Parkinson's patients, demonstrating improved motor symptoms

without severe adverse effects. This pioneering study highlights how iPSCs can be harnessed for cell replacement therapies, addressing the root cause of neurodegeneration rather than merely alleviating symptoms.

Stem cell therapies are also being explored for treating SCI, which often lead to permanent motor and sensory deficits [97]. NSCs hold particular promise in this domain due to their ability to integrate into damaged CNS tissue and differentiate into neurons, astrocytes, and oligodendrocytes [98]. A study by Hosseini et al. [99], showed that NSC transplantation into animal models of SCI led to significant functional recovery, attributed to both neural replacement and remyelination of spared axons. Translating these findings into human trials, companies like Asterias Biotherapeutics have reported encouraging outcomes with NSC-derived therapies in restoring motor function in SCI patients [100].

In neurodegenerative disorders such as Alzheimer's disease, where neuronal death and synaptic loss play a central role, stem cell-based approaches are being evaluated for their potential to slow disease progression and restore cognitive function [101]. Recent work by Marsh and Blurton-Jones [102] demonstrated that NSCs transplanted into animal models of Alzheimer's disease not only survived but also improved cognitive outcomes by enhancing synaptic density and modulating neuroinflammation. Additionally, stem cell-derived exosomes containing microRNAs and growth factors have shown promise in preclinical studies for reducing amyloid-beta plaques and tau tangles, key hallmarks of Alzheimer's disease. These findings highlight the versatility of stem cell-based therapies in addressing both structural damage and underlying pathology in neurological diseases.

Building organs from cells: Stem cells in transplantation medicine

Stem cell research is revolutionizing organ transplantation by addressing the critical shortage of donor organs and reducing the risk of immune rejection [103]. Stem cells, particularly iPSCs and MSCs, are being explored to engineer bioartificial organs and tissues. IPSCs, with their ability to differentiate into any cell type, hold the potential to generate patient-specific organoids for transplantation. For example, successfully created functional liver organoids using iPSCs, which were able to perform key metabolic functions when transplanted into animal models [104]. Such breakthroughs indicate the possibility of lab-grown organs becoming a viable alternative to organ donation.

Another critical application is in creating vascularized organs, which has been one of the greatest challenges in organ transplantation [105]. Stem cell-derived endothelial cells are being used to create networks of blood vessels within organ constructs. In a study by, researchers used iPSCs to develop vascularized kidney organoids capable of filtering waste and producing urine-like fluid. These findings bring us closer to engineering fully functional replacement organs, potentially eliminating the need for dialysis in kidney failure patients [106].

MSCs are also gaining traction for their immunomodulatory properties, which can help reduce organ rejection [107]. By suppressing the immune response and promoting tolerance, MSCs are being used as an adjunct therapy in transplantation. Clinical trials have shown that MSCs infused into kidney transplant patients can reduce the need for long-term immunosuppression. These cells act by modulating T-cell activity and enhancing graft acceptance, making them a valuable tool in improving transplant outcomes [108].

In addition to organogenesis, stem cells are being used to repair and regenerate damaged organs, reducing the need for full transplantation [109]. For example, researchers have used MSCs to restore liver function in patients with cirrhosis and acute liver failure. A study by Sun et al. [110], demonstrated that MSC transplantation could promote hepatocyte regeneration and improve liver function in animal models. Similar approaches are being developed for heart, lung, and pancreas repair, expanding the scope of regenerative therapies for end-stage organ diseases.

Despite the progress, challenges such as scalability, vascularization, and functional integration of bioengineered organs remain. To overcome these hurdles, bioengineering techniques like 3D bioprinting are being combined with stem cell technology. For instance, 3D-printed scaffolds seeded with stem cells are being developed to create structurally accurate and functional organs, such as lungs and hearts. With these innovations, stem cell research is paving the way for personalized and sustainable solutions to the organ shortage crisis, offering new hope to patients on transplant waiting lists [111].

Stem cells in action: Pioneering clinical trials and future possibilities

Translational stem cell therapy has progressed significantly in clinical settings, with numerous studies focusing on the application of stem cells for treating various diseases. One of the most notable areas of clinical research is in neurodegenerative diseases like Parkinson's disease. The Parkinson's Disease Stem Cell Trial, led by scientists at the University of California, used ESCs to develop dopaminergic neurons that were transplanted into patients' brains [112]. This study demonstrated improved motor function and provided early evidence that stem cell-derived therapies could help replenish lost neurons. Although the study showed promising results, concerns over tumor formation and immune rejection remain key challenges in translating these therapies to broader clinical practice.

In cardiovascular medicine, stem cell therapies have been investigated for their potential to repair damaged heart tissue following myocardial infarction. The REPAIR-AMI trial used BMSCs to treat patients with acute myocardial infarction [113]. Results showed improvements in left ventricular function and a reduction in infarct size, offering a new approach for repairing heart muscle. Other studies, such as the ESCORT trial, explored the use of MSCs to enhance heart regeneration, providing evidence that MSCs promote tissue repair through paracrine effects [114]. Despite these advances, variability in patient responses and the need for more robust long-term data remain significant barriers to widespread clinical adoption.

Stem cell therapies are also being tested for treating autoimmune and inflammatory disorders. The MSC in systemic sclerosis trial is one such example where MSCs were administered to patients with systemic sclerosis, a condition characterized by fibrosis and immune system dysfunction [115]. The results showed improvements in skin scores and lung function, suggesting that MSCs can modulate immune responses and help in tissue regeneration. Clinical trials for multiple sclerosis and Crohn's disease have also highlighted the immunomodulatory potential of MSCs, with studies demonstrating reduced inflammation and improved disease markers [116]. These results suggest that stem cells could be an alternative to traditional immunosuppressive treatments, potentially offering a safer and more effective option for patients.

In the field of orthopedics, stem cell therapy has been tested in clinical trials to treat musculoskeletal injuries and degenerative diseases like osteoarthritis. One such trial is the Stem Cell for Knee Osteoarthritis (SCROA) study, which tested the efficacy of MSC injections in patients

with knee osteoarthritis [117]. The findings indicated that MSC-based treatments led to reduced pain and improved joint function, with some patients experiencing cartilage regeneration. Similar trials have been conducted for SCI, where stem cells are being investigated for their ability to promote nerve regeneration and functional recovery. While these studies show great promise, challenges such as ensuring long-term stability of transplanted cells, avoiding complications like fibrosis, and scaling production remain pivotal to the success of stem cell-based therapies in clinical practice.

Stem cell therapies are being tested in the treatment of various forms of cancer, particularly for hematologic malignancies. The MSCs for hematopoietic regeneration trial explores the use of MSCs in enhancing bone marrow recovery after stem cell transplantation in leukemia patients [118]. MSCs are known to promote hematopoiesis and immune modulation, and this trial showed that MSCs can help reduce the incidence of GVHD, a common complication in HSC transplantation. The results underscore the potential of MSCs to improve patient outcomes by supporting bone marrow recovery and modulating immune responses, though long-term follow-up is necessary to ensure safety and efficacy.

In the realm of ophthalmology, stem cell therapies have made significant strides in treating degenerative retinal diseases. The retinal cell transplantation study evaluated the safety and efficacy of RPE cells derived from human iPSCs in patients with age-related macular degeneration and Stargardt disease [119]. Clinical trials, such as the one conducted by StemCells Inc., have shown that transplantation of RPE cells can stabilize vision and even partially restore retinal function [120]. These promising results indicate that stem cell-derived therapies may offer new hope for patients with retinal diseases that currently lack effective treatments. However, challenges such as ensuring long-term cell survival and preventing immune rejection remain.

Stem cell therapies have also been tested in the field of liver diseases, particularly in treating cirrhosis and acute liver failure. The stem cell therapy for acute liver failure trial explored the use of autologous BMSCs to improve liver function in patients with severe liver failure [121]. Results showed that MSCs promoted liver regeneration, improved liver function, and reduced the need for liver transplantation in some patients. These findings suggest that stem cell-based treatments may become an alternative to organ transplantation, particularly for patients who are not candidates for a liver transplant. However, the effectiveness and long-term safety of such therapies require further investigation in larger, multicenter trials.

In the area of diabetes, particularly T1D, stem cell-based therapies are being explored to regenerate insulin-producing beta cells in the pancreas. The stem cell therapy for T1D trial tested the use of stem cell-derived pancreatic islet cells in patients with T1D [122]. Preliminary studies, such as those conducted by ViaCyte, demonstrated that stem cell-derived islet cells can successfully integrate into the pancreas and restore insulin production, leading to improved blood sugar control [123]. While these results are promising, challenges such as ensuring the long-term survival and function of the transplanted cells, as well as addressing issues of immune rejection, need to be overcome before these therapies can be widely used in clinical practice.

Translational Stem Cell Therapy: Challenges and Future Directions

Stem cell therapy has demonstrated remarkable promise in treating a wide array of diseases, from neurodegenerative disorders to cardiac and musculoskeletal conditions. However, the journey from research to clinical application faces numerous challenges that hinder its full translational potential (Table 4). A major hurdle lies in ensuring the safety and efficacy of stem cell-based treatments. PSCs, such as iPSCs, carry the risk of teratoma formation if undifferentiated cells are transplanted [124]. Additionally, adult stem cells, including MSCs, often exhibit variability in their therapeutic potential depending on their source, donor characteristics, and culture conditions [125]. To address these issues, stringent quality control measures and advanced purification techniques are being developed, such as automated cell sorting and real-time molecular monitoring to detect undifferentiated or defective cells.

Another key challenge is immune rejection, particularly when using allogeneic (donor-derived) stem cells. Even when MSCs exhibit low immunogenicity, repeated infusions can trigger immune responses, reducing the therapy's effectiveness [126]. Innovative approaches like developing "universal donor" stem cells through gene editing are being pursued to overcome this limitation. For example, CRISPR-Cas9 technology has been used to knock out major histocompatibility complex proteins in stem cells, creating immune-evading cell lines [127]. These universal stem cells can potentially eliminate the need for immunosuppressive drugs and broaden access to stem cell therapies.

Scalability and reproducibility present additional obstacles in the clinical translation of stem cell therapy. Large-scale production of clinical-grade stem cells requires advanced biomanufacturing facilities and compliance with good manufacturing practice standards [128]. To meet this demand, bioreactor technologies are being optimized to cultivate stem cells in controlled environments while maintaining their functionality. Innovations like microfluidic bioreactors and 3D cell culture systems enable more efficient and scalable production, ensuring a consistent supply of high-quality cells for therapeutic applications [129]. Such sustainable approaches reduce costs and enhance the feasibility of widespread adoption of stem cell therapies.

A significant challenge lies in ensuring proper integration of stem cell-derived tissues with the host environment [130]. For example, in cardiac therapies, transplanted stem cell-derived cardiomyocytes often fail to form robust electrical connections with the native myocardium, leading to arrhythmias. To address this, bioengineering solutions such as the use of tissue scaffolds and electrical stimulation devices are being integrated with stem cell therapy. These approaches mimic the physiological conditions of the human body, guiding stem cell differentiation and improving the functional integration of transplanted cells [131]. Similarly, advancements in 3D bioprinting enable the creation of patient-specific scaffolds that enhance structural and functional compatibility.

Another area of focus is reducing the risk of tumorigenesis, particularly with PSCs. Researchers are leveraging genetic engineering and small molecule inhibitors to suppress pathways that may lead to uncontrolled cell proliferation [132]. For example, inhibitors targeting the MYC oncogene, commonly associated with tumorigenesis in iPSCs, are being integrated into differentiation protocols. Additionally, cell-free therapies using stem cell-derived exosomes and secretomes offer a safer alternative, delivering therapeutic benefits without the risks associated with live cell transplantation [133]. These acellular products retain the regenerative and immunomodulatory properties of stem cells, providing a promising direction for safer therapies.

Ethical and regulatory hurdles also play a significant role in delaying the clinical translation of stem cell therapies [134]. The use of ESCs

Table 4: Properties, challenges, limitations, examples, future prospects, and disease applications of translational stem cell therapy.

Property	Description	Challenges	Limitations	Examples	Future prospects	Disease applications
Self-renewal capacity	Ability to replicate indefinitely, maintaining a pool of stem cells for long-term tissue repair.	Ensuring stable self-renewal in transplanted cells without tumor formation or uncontrolled proliferation.	Risk of tumor formation due to uncontrolled cell division.	HSCs for blood disorders.	Development of safer protocols for maintaining self-renewal without oncogenic risk.	Leukemia, lymphoma, anemia, and blood disorders.
Differentiation potential	Ability to differentiate into multiple specialized cell types (e.g., neurons, cardiomyocytes, etc.).	Ensuring proper differentiation in a controlled manner to avoid unwanted cell types.	Difficulty in controlling differentiation pathways, leading to incomplete or incorrect differentiation.	IPSCs in regenerative medicine.	Advancing directed differentiation techniques to generate specific, functional cells in a controlled environment.	Neurodegenerative diseases (e.g., Parkinson's, ALS), heart disease, and diabetes.
Plasticity and versatility	Stem cells can be adapted for various therapeutic purposes across different organs and diseases.	Limited ability to regenerate certain tissues or organs, especially those with complex architecture.	Some tissues (e.g., complex neural or cardiac tissues) remain difficult to regenerate effectively.	MSCs for osteoarthritis and heart repair.	Ongoing research to improve tissue integration and enhance regenerative potential in complex tissues.	Osteoarthritis, Muscle Degeneration, and cardiovascular diseases.
Immunomodulation	Potential to modulate immune responses, offering treatment for autoimmune diseases and reducing transplant rejection.	Potential immune rejection of transplanted stem cells, particularly in allogeneic transplants.	Allogeneic stem cell therapies may require immunosuppressive treatments, increasing the risk of infections and complications.	MSCs for autoimmune diseases (e.g., multiple sclerosis).	Developing immune-tolerant stem cells (e.g., iPSCs derived from patient cells) to avoid immune rejection and reduce therapy costs.	Multiple sclerosis, rheumatoid arthritis, organ transplantation, and GVHD.
Regenerative potential	Potential to regenerate damaged tissues, restore organ function, and improve patient outcomes.	Low engraftment and integration into the damaged tissue.	Low survival rates and functional integration of transplanted stem cells into target tissues, particularly after injury.	NSCs in spinal cord injury models.	Engineering more robust stem cell lines with improved homing and survival in damaged tissues, enhancing long-term benefits.	Spinal cord injury, osteoarthritis, liver cirrhosis, and heart failure.
Ethical considerations	Stem cell therapies, especially with ESCs, offer high developmental potential.	Ethical concerns regarding the use of ESCs and manipulation of human embryos.	Legal and ethical hurdles surrounding the use of ESCs, particularly in some regions.	ESC-derived RPE cells for macular degeneration.	Development of alternatives, such as iPSCs, to bypass ethical concerns and provide personalized therapies.	Macular degeneration, Parkinson's disease, and heart disease.
Scalability	Potential for large-scale production of stem cells for therapeutic use.	Difficulty in large-scale production and maintaining cell quality for clinical use.	Manufacturing challenges, including cost-effectiveness and consistency in large-scale production.	HSC transplantation for leukemia.	Advanced bioreactor technologies and scalable protocols to streamline the production of high-quality stem cells at reduced cost.	Leukemia, bone regeneration, and cardiovascular disease.

has been met with ethical concerns, prompting the shift toward iPSCs, which avoid these controversies. However, regulatory frameworks must evolve to keep pace with advances in stem cell technologies. Streamlined approval processes, harmonized global regulations, and increased funding for clinical trials are crucial to accelerate the transition of innovative therapies from bench to bedside. Public engagement and education are also essential to address misconceptions and foster acceptance of stem cell-based treatments [135].

Looking ahead, the future of stem cell therapy lies in interdisciplinary collaboration among stem cell biology, bioengineering, and data science. Artificial intelligence and machine learning are being harnessed to optimize cell culture conditions, predict therapeutic outcomes, and identify biomarkers for patient selection. Furthermore, combining stem cell therapy with gene editing and advanced biomaterials can address current limitations and open new frontiers in personalized and regenerative medicine. By embracing innovation and sustainable approaches, the field is poised to overcome existing challenges and deliver transformative therapies for a wide range of diseases.

Conclusions

Stem cell therapy holds immense promises for the treatment of a wide range of human diseases, offering potential solutions to previously untreatable conditions. From neurodegenerative diseases like Parkinson's and Alzheimer's, to cardiovascular disorders, diabetes, and even certain cancers, stem cells have demonstrated their capacity to repair damaged tissues, regenerate organs, and improve patient outcomes. With advances in PSC technologies, such as iPSCs, as well as the use of adult stem cells like MSCs, we are witnessing significant strides in developing personalized treatments that address the root causes of these diseases, rather than just managing symptoms. Clinical trials are increasingly showing promising results, offering hope for patients and families affected by chronic and life-threatening conditions.

However, the translation of stem cell therapies into widespread clinical use is not without its challenges. Issues such as immune rejection, ethical concerns, scalability of production, and long-term safety need to be carefully addressed. Continued research, rigorous clinical trials, and innovation in gene editing, cell manufacturing, and immune tolerance are crucial to overcoming these hurdles. As these challenges are met, stem cell therapies have the potential to not only improve individual patient welfare but also transform the healthcare landscape, providing more effective, sustainable, and personalized treatments for a broad range of diseases. With ongoing advancements, stem cell therapy is poised to significantly enhance the quality of life and overall health outcomes for millions of people around the world.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Ávila-González D, Gidi-Grenat MÁ, García-López G, Martínez-Juárez A, Molina-Hernández A, et al. (2023) Pluripotent stem cells as a model for human embryogenesis. Cells 12: 1192. https://doi.org/10.3390/cells12081192

2. Karima G, Kim HD (2024) Unlocking the regenerative key: targeting stem cell factors for bone renewal. J Tissue Eng 15: 1-26. https://doi.org/10.1177/20417314241287491

3. Hoang DM, Pham PT, Bach TQ, Ngo AT, Nguyen QT, et al. (2022) Stem cell-based therapy for human diseases. Signal Transduct Target Ther 7: 1-41. https://doi.org/10.1038/s41392-022-01134-4

4. Wei L, Yan W, Shah W, Zhang Z, Wang M, et al. (2024) Advancements and challenges in stem cell transplantation for regenerative medicine. Heliyon 10: 1-21. https://doi.org/10.1016/j.heliyon.2024.e35836

5. Rehman A, Fatima I, Noor F, Qasim M, Wang P, et al. (2024) Role of small molecules as drug candidates for reprogramming somatic cells into induced pluripotent stem cells: a comprehensive review. Comput Biol Medn 177: 108661. https://doi.org/10.1016/j.compbiomed.2024.108661

6. Golchin A, Shams F, Moradi F, Sadrabadi AE, Parviz S, et al. (2025) Single-cell technology in stem cell research. Curr Stem Cell Res Ther 20: 9–32. https://doi.org/10.2174/011574888x265479231127065541

7. Velikic G, Maric DM, Maric DL, Supic G, Puletic M, et al. (2024) Harnessing the stem cell niche in regenerative medicine: Innovative avenue to combat neurodegenerative diseases. Int J Mol Sci 25: 993. https://doi.org/10.3390/ijms25020993

8. Chowdhury S, Ghosh S, Chowdhury S, Ghosh S (2021) Stem cells in clinical research and therapy. Stem Cells Biol Ther 2021: 239-252. https://doi.org/10.1007/978-981-16-1638-9_10

9. Silva-Pedrosa R, Salgado AJ, Ferreira PE (2023) Revolutionizing disease modeling: the emergence of organoids in cellular systems. Cells 12: 930. https://doi.org/10.3390/cells12060930

10. Azar J, Bahmad HF, Daher D, Moubarak MM, Hadadeh O, et al. (2021) The use of stem cell-derived organoids in disease modeling: an update. Int J Mol Sci 22: 7667. https://doi.org/10.3390/ijms22147667

11. Bashor CJ, Hilton IB, Bandukwala H, Smith DM, Veiseh O (2022) Engineering the next generation of cell-based therapeutics. Nat Rev Drug Discov 21: 655-675. https://doi.org/10.1038/s41573-022-00476-6

12. da Silva RGL (2024) The advancement of artificial intelligence in biomedical research and health innovation: challenges and opportunities in emerging economies. Global Health 20: 1-19. https://doi.org/10.1186/s12992-024-01049-5

13. Bhattacharjee G, Gohil N, Khambhati K, Mani I, Maurya R, et al. (2022) Current approaches in CRISPR-Cas9 mediated gene editing for biomedical and therapeutic applications. J Control Release 343: 703-723. https://doi.org/10.1016/j.jconrel.2022.02.005

14. Zeng CW (2023) Advancing spinal cord injury treatment through stem cell therapy: a comprehensive review of cell types, challenges, and emerging technologies in regenerative medicine. Int J Mol Sci 24: 14349. https://doi.org/10.3390/ijms241814349

15. Sarkar A, Saha S, Paul A, Maji A, Roy P, et al. (2021) Understanding stem cells and its pivotal role in regenerative medicine. Life Sci 273: 119270. https://doi.org/10.1016/j.lfs.2021.119270

16. Ponnusamy B, Rajagopal P, Panneerselvam S, Veeraraghavan V, Jayaraman S (2024) Stem cell–based approach in treatment of periodontitis. In Stem Cells and Signaling Pathways. Academic Press, pp 301–315.

17. Priester C, MacDonald A, Dhar M, Bow A (2020) Examining the characteristics and applications of mesenchymal, induced pluripotent, and embryonic stem cells for tissue engineering approaches across the germ layers. Pharmaceuticals 13: 344. https://doi.org/10.3390/ph13110344

18. Luo Y, Yu Y (2022) Research advances in gametogenesis and embryogenesis using pluripotent stem cells. Front Cell Dev Biol 9: 1-14. https://doi.org/10.3389/fcell.2021.801468

19. Sezaki M, Hayashi Y, Wang Y, Johansson A, Umemoto T, et al. 2020. Immunomodulation of hematopoietic stem and progenitor cells in inflammation. Front Immunol 11: 1-16. https://doi.org/10.3389/fimmu.2020.585367

20. Díaz-García D, Filipová A, Garza-Veloz I, Martinez-Fierro ML (2021) A beginner's introduction to skin stem cells and wound healing. Int J Mol Sci 22: 11030. https://doi.org/10.3390/ijms222011030

21. Nóbrega C, Mendonça L, Matos CA (2020) Stem cells and tissue regeneration. In A Handbook of Gene and Cell Therapy.

22. Hayward MK, Muncie JM, Weaver VM (2021) Tissue mechanics in stem cell fate, development, and cancer. Dev Cell 56: 1833-1847. https://doi.org/10.1016/j.devcel.2021.05.011

23. Liebing E, Krug SM, Neurath MF, Siegmund B, Becker C (2024) Wall of resilience: How the intestinal epithelium prevents inflammatory onslaught in the gut. Cell Mol Gastroenterol Hepatol 19: 101423. https://doi.org/10.1016/j.jcmgh.2024.101423

24. Sousa-Victor P, García-Prat L, Muñoz-Cánoves P (2022) Control of satellite cell function in muscle regeneration and its disruption in ageing. Nat Rev Mol Cell Biol 23: 204-226. https://doi.org/10.1038/s41580-021-00421-2

25. Hybiak J, Jankowska K, Machaj F, Rosik J, Broniarek I, et al. (2020) Reprogramming and transdifferentiation-two key processes for regenerative medicine. Eur J Pharmacol 882: 173202. https://doi.org/10.1016/j.ejphar.2020.173202

26. Meir YJJ, Li G (2021) Somatic reprogramming-Above and beyond pluripotency. Cells 10: 2888. https://doi.org/10.3390/cells10112888

27. Han F, Liu Y, Huang J, Zhang X, Wei C (2021) Current approaches and molecular mechanisms for directly reprogramming fibroblasts into neurons and dopamine neurons. Front Aging Neurosci 13: 1-13. https://doi.org/10.3389/fnagi.2021.738529

28. Kumar R, Jastrzębska AM, Cucchiarin M, Chhillar N, Chhillar M (2024) Computational and stem cell biology: challenges and future perspectives. In Computational Biology for Stem Cell Research. Academic Press, pp 85–104.

29. Riether C (2022) Regulation of hematopoietic and leukemia stem cells by regulatory T cells. Front Immunol 13: 1-15. https://doi.org/10.3389/fimmu.2022.1049301

30. Brunet A, Goodell MA, Rando TA (2023) Ageing and rejuvenation of tissue stem cells and their niches. Nat Rev Mol Cell Biol 24: 45–62. https://doi.org/10.1038/s41580-022-00510-w

31. Chandel NS, Jasper H, Ho TT, Passegue E (2016) Metabolic regulation of stem cell function in tissue homeostasis and organismal ageing. Nature Cell Biol 18: 823-832. https://doi.org/10.1038/ncb3385

32. Hussen BM, Taheri M, Yashooa RK, Abdullah GH, Abdullah SR, et al. (2024) Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. Int J Surg 110: 8002-8024. https://doi.org/10.1097/JS9.0000000000002109

33. Giommetti A, Papanikolaou E (2024) Advancements in hematopoietic stem cell gene therapy: a journey of progress for viral transduction. Cells 13: 1039. https://doi.org/10.3390/cells13121039

34. Koniali L, Lederer CW, Kleanthous M (2021) Therapy development by genome editing of hematopoietic stem cells. Cells 10: 1492. https://doi.org/10.3390/cells10061492

35. Mesenchymal Stem Cells (MSC) Harvesting. [https://www.drrobertwhitfield.com/mesenchymal-stem-cells-mscs-harvesting/] [Accessed February 23, 2025]

36. Huang Y, Wu Q, Tam PK (2022) Immunomodulatory mechanisms of mesenchymal stem cells and their potential clinical applications. Int J Mol Sci 23: 10023. https://doi.org/10.3390/ijms231710023

37. Xie Q, Liu R, Jiang J, Peng J, Yang C, et al. (2020) What is the impact of human umbilical cord mesenchymal stem cell transplantation on clinical treatment?. Stem cell Res Ther 11: 1-3. https://doi.org/10.1186/s13287-020-02011-z

38. Galderisi U, Peluso G, Di Bernardo G (2022) Clinical trials based on mesenchymal stromal cells are exponentially increasing: where are we in recent years?. Stem Cell Rev Rep 18: 23-36. https://doi.org/10.1007/s12015-021-10231-w

39. Michniacki TF, Choi SW, Peltier DC (2021) Immune Suppression in Allogeneic Hematopoietic Stem Cell Transplantation. In Pharmacology of Immunosuppression. Springer International Publishing, pp 209-243.

40. Hwang JJ, Rim YA, Nam Y, Ju JH (2021) Recent developments in clinical applications of mesenchymal stem cells in the treatment of rheumatoid arthritis and osteoarthritis. Front Immunol 12: 631291. https://doi.org/10.3389/fimmu.2021.631291

41. Rubinato L, Redolfi de Zan E, Sarao V, Veritti D, Lanzetta P (2024) Stem cell therapy in retinal diseases: current evidence. Exp Rev Ophthalmol 19: 119-131. https://doi.org/10.1080/17469899.2023.2296895

42. Shah S, Tereda A, Mansour HM (2024) Molecular mechanisms of degeneration in parkinson's disease; deep brain stimulation, pluripotent stem cell therapy, and cutting edge technology in treatment of parkinson's disease. Curr Genet Med Rep 12: 1-9. https://doi.org/10.1007/s40142-024-00210-1

43. Li Y, Xu M, Chen J, Huang J, Cao J, et al. (2024) Ameliorating and refining islet organoids to illuminate treatment and pathogenesis of diabetes mellitus. Stem Cell Res Ther 15: 188. https://doi.org/10.1186/s13287-024-03780-7

44. Zhou Z, Cong L, Cong X (2021) Patient-derived organoids in precision medicine: drug screening, organoid-on-a-chip and living organoid biobank. Front Oncol 11: 762184. https://doi.org/10.3389/fonc.2021.762184

45. Morotti M, Albukhari A, Alsaadi A, Artibani M, Brenton JD, et al. (2021) Promises and challenges of adoptive T-cell therapies for solid tumours. Br J Cancer 124: 1759-1776. https://doi.org/10.1038/s41416-021-01353-6

46. Skidmore S, Barker RA (2023) Challenges in the clinical advancement of cell therapies for Parkinson's disease. Nat Biomed Eng 7: 370-386. https://doi.org/10.1038/s41551-022-00987-y

47. Haworth R, Sharpe M (2021) Accept or reject: the role of immune tolerance in the development of stem cell therapies and possible future approaches. Toxicol Pathol 49: 1308-1316. https://doi.org/10.1177/0192623320918241

48. Khanna A, Ayan B, Undieh AA, Yang YP, Huang NF (2022) Advances in three-dimensional bioprinted stem cell-based tissue engineering for cardiovascular regeneration. J Mol Cell Cardiol 169: 13-27. https://doi.org/10.1016/j.yjmcc.2022.04.017

49. Okeke C, Silas U, Okeke C, Chikwendu C (2021) Current trends on hemopoietic stem cells. Curr Stem Cell Res Ther 16: 199-208. https://doi.org/10.2174/1574888X15999200729162021

50. Sankar V, Villa A (2021) Hematologic diseases. In Burket's Oral Medicine, pp 627-664.

51. Ciurea SO, Al Malki MM, Kongtim P, Fuchs EJ, Luznik L, et al. (2020) The European society for blood and marrow transplantation (EBMT) consensus recommendations for donor selection in haploidentical hematopoietic cell transplantation. Bone Marrow Transplant 55: 12-24. https://doi.org/10.1038/s41409-019-0499-z

52. Anurogo D, Yuli Prasetyo Budi N, Thi Ngo MH, Huang YH, Pawitan JA (2021) Cell and gene therapy for anemia: hematopoietic stem cells and gene editing. Int J Mol Sci 22: 6275. https://doi.org/10.3390/ijms22126275

53. Bhattacharjee G, Gohil N, Khambhati K, Mani I, Maurya R, et al. (2022) Current approaches in CRISPR-Cas9 mediated gene editing for biomedical and therapeutic applications. J Contr Release 343: 703-723. https://doi.org/10.1016/j.jconrel.2022.02.005

54. Germino-Watnick P, Hinds M, Le A, Chu R, Liu X, et al. (2022) Hematopoietic stem cell gene-addition/editing therapy in sickle cell disease. Cells 11: 1843. https://doi.org/10.3390/cells11111843

55. Cavazzana M, Corsia A, Brusson M, Miccio A, Semeraro M (2024) Treating sickle cell disease: gene therapy approaches. Annu Rev Pharmacol Toxicol 65: 397-413. https://doi.org/10.1146/annurev-pharmtox-022124-022000

56. Műzes G, Sipos F (2022) Mesenchymal stem cell-derived secretome: a potential therapeutic option for autoimmune and immune-mediated inflammatory diseases. Cells 11: 2300. https://doi.org/10.3390/cells11152300

57. Wang S, Lei B, Zhang E, Gong P, Gu J, et al. (2022) Targeted therapy for inflammatory diseases with mesenchymal stem cells and their derived exosomes: from basic to clinics. Int J Nanomed 17: 1757-1781.

58. Introna M, Golay J (2020) Tolerance to bone marrow transplantation: do mesenchymal stromal cells still have a future for acute or chronic GvHD?. Front Immunol 11: 609063. https://doi.org/10.3389/fimmu.2020.609063

59. Yan D, Zhan S, Guo C, Han J, Zhan L, et al. (2024) The role of myocardial regeneration, cardiomyocyte apoptosis in acute myocardial infarction: a review of current research trends and challenges. J Cardiol, In Press. https://doi.org/10.1016/j.jjcc.2024.09.012

60. Barreca MM, Cancemi P, Geraci F (2020) Mesenchymal and induced pluripotent stem cells-derived extracellular vesicles: the new frontier for regenerative medicine?. Cells 2020 9: 1163. https://doi.org/10.3390/cells9051163

61. Dehghan S, Mirshahi R, Shoae-Hassani A, Naseripour M (2022) Human-induced pluripotent stem cells-derived retinal pigmented epithelium, a new horizon for cells-based therapies for age-related macular degeneration. Stem Cell Res Ther 13: 217. https://doi.org/10.1186/s13287-022-02894-0

62. Antonov SA, Novosadova EV (2021) Current state-of-the-art and unresolved problems in using human induced pluripotent stem cell-derived dopamine neurons for parkinson's disease drug development. Int J Mol Sci 22: 3381. https://doi.org/10.3390/ijms22073381

63. Fang M, Allen A, Luo C, Finn JD (2024) Unlocking the potential of iPSC-derived immune cells: Engineering iNK and iT cells for cutting-edge immunotherapy. Front Immunol 15: 1457629. https://doi.org/10.3389/fimmu.2024.1457629

64. Han X, Cai C, Deng W, Shi Y, Li L, et al. (2024) Landscape of human organoids: Ideal model in clinics and research. Innovation 5: 100620. https://doi.org/10.1016/j.xinn.2024.100620

65. Pranty AI, Shumka S, Adjaye J (2022) Bilirubin-induced neurological damage: current and emerging iPSC-derived brain organoid models. Cells 11: 2647. https://doi.org/10.3390/cells11172647

66. Kim SH, Chang MY (2023) Application of human brain organoids—opportunities and challenges in modeling human brain development and neurodevelopmental diseases. Int J Mol Sci 24: 12528. https://doi.org/10.3390/ijms241512528

67. Heaton ES, Jin S (2022) Importance of multiple endocrine cell types in islet organoids for type 1 diabetes treatment. Transl Res 250: 68-83. https://doi.org/10.1016/j.trsl.2022.06.014

68. Nikokiraki C, Psaraki A, Roubelakis MG (2022) The potential clinical use of stem/progenitor cells and organoids in liver diseases. Cells 11: 1410. https://doi.org/10.3390/cells11091410

69. Paolini Sguazzi G, Muto V, Tartaglia M, Bertini E, Compagnucci C (2021) Induced pluripotent stem cells (iPSCs) and gene therapy: a new era for the treatment of neurological diseases. Int J Mol Sci 22: 13674. https://doi.org/10.3390/ijms222413674

70. Pena SA, Iyengar R, Eshraghi RS, Bencie N, Mittal J, et al. (2020) Gene therapy for neurological disorders: challenges and recent advancements. J Drug Target 28: 111-128. https://doi.org/10.1080/1061186X.2019.1630415

71. Ferrari G, Thrasher AJ, Aiuti A (2021) Gene therapy using haematopoietic stem and progenitor cells. Nat Rev Genet 22: 216-234. https://doi.org/10.1038/s41576-020-00298-5

72. Johns AE, Maragakis NJ (2022) Exploring motor neuron diseases using iPSC platforms. Stem Cells 40: 2-13. https://doi.org/10.1093/stmcls/sxab006

73. Al Abbar A, Ngai SC, Nograles N, Alhaji SY, Abdullah S (2020) Induced pluripotent stem cells: reprogramming platforms and applications in cell replacement therapy. Bio Res 9: 121-136. https://doi.org/10.1089/biores.2019.0046

74. Parrotta EI, Lucchino V, Scaramuzzino L, Scalise S, Cuda G (2020) Modeling cardiac disease mechanisms using induced pluripotent stem cell-derived cardiomyocytes: progress, promises and challenges. Int J Mol Sci 21: 4354. https://doi.org/10.3390/ijms21124354

75. Chang C, Yan J, Yao Z, Zhang C, Li X, et al. (2021) Effects of mesenchymal stem cell-derived paracrine signals and their delivery strategies. Adv Healthc Mater 10: 2001689. https://doi.org/10.1002/adhm.202001689

76. Czulada E, Tang T, Seau Q, Lankipelle N (2022) Factors affecting outcomes of bone marrow stem cell therapy for acute myocardial infarction. Georgetown Med Rev 6.

77. Afjeh-Dana E, Naserzadeh P, Moradi E, Hosseini N, Seifalian AM, et al. (2022) Stem cell differentiation into cardiomyocytes: current methods and emerging approaches. Stem Cell Revi Rep 18: 2566-2592. https://doi.org/10.1007/s12015-021-10280-1

78. Wang L, Serpooshan V, Zhang J (2021) Engineering human cardiac muscle patch constructs for prevention of post-infarction LV remodeling. Front Cardiovasc Med 8: 621781. https://doi.org/10.3389/fcvm.2021.621781

79. Le DC, Bui HT, Vu YT, Vo QD (2024) Induced pluripotent stem cell therapies in heart failure treatment: a meta-analysis and systematic review. Regen Med 19: 497-509. https://doi.org/10.1080/17460751.2024.2393558

80. Liu N, Ye X, Yao B, Zhao M, Wu P, et al. (2021) Advances in 3D bioprinting technology for cardiac tissue engineering and regeneration. Bioact Mater 6: 1388-1401. https://doi.org/10.1016/j.bioactmat.2020.10.021

81. Cho HM, Cho JY (2021) Cardiomyocyte death and genome-edited stem cell therapy for ischemic heart disease. Stem Cell Rev Rep 17: 1-6. https://doi.org/10.1007/s12015-020-10096-5

82. Kolimi P, Narala S, Nyavanandi D, Youssef AA, Dudhipala N (2022) Innovative treatment strategies to accelerate wound healing: trajectory and recent advancements. Cells 11: 2439. https://doi.org/10.3390/cells11152439

83. Krawczenko A, Klimczak A (2022) Adipose tissue-derived mesenchymal stem/stromal cells and their contribution to angiogenic processes in tissue regeneration. Int J Mol Sci 23: 2425. https://doi.org/10.3390/ijms23052425

84. Dash BC, Korutla L, Vallabhajosyula P, Hsia HC (2022) Unlocking the potential of induced pluripotent stem cells for wound healing: the next frontier of regenerative medicine. Adv Wound Care 11: 622-638. https://doi.org/10.1089/wound.2021.0049

85. Malhotra P, Shukla M, Meena P, Kakkar A, Khatri N, et al. (2021) Mesenchymal stem cells are prospective novel off-the-shelf wound management tools. Drug Deliv Transl Res 12: 1-26. https://doi.org/10.1007/s13346-021-00925-6

86. Hong ZX, Zhu ST, Li H, Luo JZ, Yang Y, et al. (2023) Bioengineered skin organoids: from development to applications. Mil Med Res 10: 40. https://doi.org/10.1186/s40779-023-00475-7

87. Mahajan N, Soker S, Murphy SV (2024) Regenerative medicine approaches for skin wound healing: from allografts to engineered skin substitutes. Curr Transplant Rep 11: 207-221. https://doi.org/10.1007/s40472-024-00453-5

88. Shokrani H, Shokrani A, Sajadi SM, Seidi F, Mashhadzadeh AH, et al. (2022) Cell-seeded biomaterial scaffolds: the urgent need for unanswered accelerated angiogenesis. Int J Nanomed 17: 1035-1068.

89. Qin J, Chen F, Wu P, Sun G (2022) Recent advances in bioengineered scaffolds for cutaneous wound healing. Front Bioeng Biotechnol 10: 841583. https://doi.org/10.3389/fbioe.2022.841583

90. Beheshtizadeh N, Gharibshahian M, Pazhouhnia Z, Rostami M, Zangi AR, et al. (2022) Commercialization and regulation of regenerative medicine products: Promises, advances and challenges. Biomed Pharmacother 153: 113431. https://doi.org/10.1016/j.biopha.2022.113431

91. Ma H, Siu WS, Leung PC (2023) The potential of MSC-based cell-free therapy in wound healing—a thorough literature review. Int J Mol Sci 24: 9356. https://doi.org/10.3390/ijms24119356

92. Kaminska A, Radoszkiewicz K, Rybkowska P, Wedzinska A, Sarnowska A (2022) Interaction of neural stem cells (NSCs) and mesenchymal stem cells (MSCs) as a promising approach in brain study and nerve regeneration. Cells 11: 1464. https://doi.org/10.3390/cells11091464

93. Zha K, Yang Y, Tian G, Sun Z, Yang Z, et al. (2021) Nerve growth factor (NGF) and NGF receptors in mesenchymal stem/stromal cells: Impact on potential therapies. Stem Cells Transl Med 10: 1008-1020. https://doi.org/10.1002/sctm.20-0290

94. Smith JA, Nicaise AM, Ionescu RB, Hamel R, Peruzzotti-Jametti L, et al. (2021) Stem cell therapies for progressive multiple sclerosis. Front Cell Dev Biol 9: 696434. https://doi.org/10.3389/fcell.2021.696434

95. McTague A, Rossignoli G, Ferrini A, Barral S, Kurian MA (2021) Genome editing in iPSC-based neural systems: from disease models to future therapeutic strategies. Front Genome Ed 3: 630600. https://doi.org/10.3389/fgeed.2021.630600

96. Takahashi J (2020) iPS cell-based therapy for Parkinson's disease: a Kyoto trial. Regen Ther 13: 18-22. https://doi.org/10.1016/j.reth.2020.06.002

97. Silvestro S, Bramanti P, Trubiani O, Mazzon E (2020) Stem cells therapy for spinal cord injury: an overview of clinical trials. Int J Mol Sci 21: 659. https://doi.org/10.3390/ijms21020659

98. Willis CM, Nicaise AM, Peruzzotti-Jametti L, Pluchino S (2020) The neural stem cell secretome and its role in brain repair. Brain Res 1729: 146615. https://doi.org/10.1016/j.brainres.2019.146615

99. Hosseini SM, Borys B, Karimi-Abdolrezaee S (2024) Neural stem cell therapies for spinal cord injury repair: an update on recent preclinical and clinical advances. Brain 147: 766-793. https://doi.org/10.1093/brain/awad392

100. Shen H, Fan C, You Z, Xiao Z, Zhao Y, et al. (2022) Advances in biomaterial-based spinal cord injury repair. Adv Funct Mater 32: 2110628. https://doi.org/10.1002/adfm.202110628

101. Cecerska-Heryć E, Pękała M, Serwin N, Gliźniewicz M, Grygorcewicz B, et al. (2023) The use of stem cells as a potential treatment method for selected neurodegenerative diseases. Cell Mol Neurobiol 43: 2643-2673. https://doi.org/10.1007/s10571-023-01344-6

102. Marsh SE, Blurton-Jones M (2017) Neural stem cell therapy for neurodegenerative disorders: the role of neurotrophic support. Neurochem Int 106: 94-100. https://doi.org/10.1016/j.neuint.2017.02.006

103. Mahla RS (2016) Stem cells applications in regenerative medicine and disease therapeutics. Int J Cell Biol 2016. https://doi.org/10.1155/2016/6940283

104. Reza HA, Okabe R, Takebe T (2021) Organoid transplant approaches for the liver. Transpl Int 34: 2031-2045. https://doi.org/10.1111/tri.14128

105. Hussein KH, Park KM, Yu L, Song SH, Woo HM, et al. (2020) Vascular reconstruction: a major challenge in developing a functional whole solid organ graft from decellularized organs. Acta Biomater 103: 68-80. https://doi.org/10.1016/j.actbio.2019.12.029

106. Lim DS, Jackson JD, Atala A, Yoo JJ (2022) Leading approaches to vascularize kidney constructs in tissue engineering. Engineering 19: 117-127. https://doi.org/10.1016/j.eng.2022.05.004

107. Deo D, Marchioni M, Rao P (2022) Mesenchymal stem/stromal cells in organ transplantation. Pharmaceutics 14: 791. https://doi.org/10.3390/pharmaceutics14040791

108. Casiraghi F, Perico N, Gotti E, Todeschini M, Mister M, et al. (2020) Kidney transplant tolerance associated with remote autologous mesenchymal stromal cell administration. Stem Cells Transl Med 9: 427-432. https://doi.org/10.1002/sctm.19-0185

109. Jiang LL, Li H, Liu L (2021) Xenogeneic stem cell transplantation: research progress and clinical prospects. World J Clin Cases 9: 3826. http://dx.doi.org/10.12998/wjcc.v9.i16.3826

110. Sun H, Shi C, Ye Z, Yao B, Li C, et al. (2022) The role of mesenchymal stem cells in liver injury. Cell Biol Int 46: 501-511. https://onlinelibrary.wiley.com/doi/full/10.1002/cbin.11725

111. Mills PA, Mills DK (2020) Reduced supply in the organ donor market and how 3D printing can address this shortage: a critical inquiry into the collateral effects of driverless cars. Appl Sci 10: 6400. https://doi.org/10.3390/app10186400

112. Can Dopamine be Restored in Parkinson's Patients? [https://www.ucihealth.org/blog/2024/01/restoring-dopamine-in-parkinsons-patients] [Accessed February 23, 2025]

113. Hamshere S, Choudhury T, Jones DA, Locca D, Mills P, et al. (2014) A randomised double-blind control study of early intracoronary autologous bone marrow cell infusion in acute myocardial infarction (REGENERATE-AMI). BMJ Open 4: e004258.

114. Zhang J, Bolli R, Garry DJ, Marbán E, Menasché P, et al. (2021) Basic and translational research in cardiac repair and regeneration: JACC state-of-the-art review. J Am Coll Cardiol 78: 2092-2105. https://doi.org/10.1016/j.jacc.2021.09.019

115. Rozier P, Maria A, Goulabchand R, Jorgensen C, Guilpain P, et al. (2018) Mesenchymal stem cells in systemic sclerosis: allogenic or autologous approaches for therapeutic use?. Front Immunol 9: 2938. https://doi.org/10.3389/fimmu.2018.02938

116. Zhao Q, Ren H, Han Z (2016) Mesenchymal stem cells: immunomodulatory capability and clinical potential in immune diseases. J Cell Immunother 2: 3-20. https://doi.org/10.1016/j.jocit.2014.12.001

117. Stem Cell Therapy for Osteoarthritis Reviewed in MILES Study. [https://physicians.dukehealth.org/articles/stem-cell-therapy-osteoarthritis-reviewed-miles-study] [Accessed February 23, 2025]

118. Burnham AJ, Daley-Bauer LP, Horwitz EM (2020) Mesenchymal stromal cells in hematopoietic cell transplantation. Blood Adv 4: 5877-5887. https://doi.org/10.1182/bloodadvances.2020002646

119. Alcalde I, Sánchez-Fernández C, Martín C, De Pablo N, Jemni-Damer N, et al. (2022) Human stem cell transplantation for retinal degenerative diseases: where are we now?. Medicina 58: 102. https://doi.org/10.3390/medicina58010102

120. Liu Z, Parikh BH, Tan QS, Wong DS, Ong KH, et al. (2021) Surgical transplantation of human RPE stem cell-derived RPE monolayers into non-human primates with immunosuppression. Stem Cell Rep 16: 237-251. https://doi.org/10.1016/j.stemcr.2020.12.007

121. Wang YH, Chen EQ (2023) Mesenchymal stem cell therapy in acute liver failure. Gut Liver 17: 674.

122. De Klerk E, Hebrok M (2021) Stem cell-based clinical trials for diabetes mellitus. Front Endocrinol 12: 631463. https://doi.org/10.3389/fendo.2021.631463

123. Ramzy A, Belmonte PJ, Braam MJ, Ida S, Wilts EM, et al. (2023) A century-long journey from the discovery of insulin to the implantation of stem cell–derived islets. Endocr Rev 44: 222-253. https://doi.org/10.1210/endrev/bnac021

124. Fong CY, Gauthaman K, Bongso A (2010) Teratomas from pluripotent stem cells: a clinical hurdle. J Cell Biochem 111: 769-781. https://doi.org/10.1002/jcb.22775

125. Costa LA, Eiro N, Fraile M, Gonzalez LO, Saá J, et al. (2021) Functional heterogeneity of mesenchymal stem cells from natural niches to culture conditions: implications for further clinical uses. Cell Mol Life Sci 78: 447-467. https://doi.org/10.1007/s00018-020-03600-0

126. Griffin MD, Ritter T, Mahon BP (2010) Immunological aspects of allogeneic mesenchymal stem cell therapies. Hum Gene Ther 21: 1641-1655. https://doi.org/10.1089/hum.2010.156

127. Meissner TB, Schulze HS, Dale SM (2022) Immune editing: overcoming immune barriers in stem cell transplantation. Curr Stem Cell Rep 8: 206-218. https://doi.org/10.1007/s40778-022-00221-0

128. Jayaraman P, Lim R, Ng J, Vemuri MC (2021) Acceleration of translational mesenchymal stromal cell therapy through consistent quality GMP manufacturing. Front Cell Dev Biol 9: 648472. https://doi.org/10.3389/fcell.2021.648472

129. Ge C, Selvaganapathy PR, Geng F (2023) Advancing our understanding of bioreactors for industrial-sized cell culture: health care and cellular agriculture implications. Am J Physiol Cell Physiol 325: 580-591. https://doi.org/10.1152/ajpcell.00408.2022

130. Wiles K, Fishman JM, De Coppi P, Birchall MA (2016) The host immune response to tissue-engineered organs: current problems and future directions. Tissue Eng Part B Rev 22: 208-219. https://doi.org/10.1089/ten.teb.2015.0376

131. Higuchi A, Ling QD, Chang Y, Hsu ST, Umezawa A (2013) Physical cues of biomaterials guide stem cell differentiation fate. Chem Rev 113: 3297-3328.

132. Cubillos-Ruiz A, Guo T, Sokolovska A, Miller PF, Collins JJ, et al. (2021) Engineering living therapeutics with synthetic biology. Nat Rev Drug Discov 20: 941-960. https://doi.org/10.1038/s41573-021-00285-3

133. Aldoghachi AF, Chong ZX, Yeap SK, Cheong SK, Ho WY, et al. (2023) Stem cells for cancer therapy: translating the uncertainties and possibilities of stem cell properties into opportunities for effective cancer therapy. Int J Mol Sci 24: 1012. https://doi.org/10.3390/ijms24021012

134. Hejrati N, Wong R, Khazaei M, Fehlings MG (2023) How can clinical safety and efficacy concerns in stem cell therapy for spinal cord injury be overcome?. Expert Opin Biol Ther 23: 883-899. https://doi.org/10.1080/14712598.2023.2245321

135. Qiu T, Liang S, Wang Y, Dussart C, Borissov B, et al. (2021) Reinforcing collaboration and harmonization to unlock the potentials of advanced therapy medical products: future efforts are awaited from manufacturers and decision-makers. Front Public Health 9: 754482. https://doi.org/10.3389/fpubh.2021.754482