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REVIEW ARTICLE

Harnessing stem cells for regenerative medicine: Current applications and future prospects

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Abstract

Background: Degenerative diseases place an immense burden on global healthcare. Stem cell-based regenerative medicine offers transformative, potentially curative therapies to restore damaged tissues and recover normal physiological function. **Aim:** This review aims to comprehensively evaluate the therapeutic applications, biological mechanisms, and clinical prospects of stem cells in treating diverse human organ disorders. **Methods:** We conducted a comprehensive literature review of preclinical models and clinical trials focusing on mesenchymal (MSCs), hematopoietic (HSCs), and pluripotent stem cells (PSCs), evaluating their efficacy, safety, and manufacturing challenges. **Results:** Cell therapies demonstrate remarkable healing potential. MSCs exhibit potent immunomodulatory effects in inflammatory conditions. HSC transplantation remains the gold standard for hematological disorders and is expanding into targeted gene therapies. PSC-derived cells show promising clinical efficacy in spinal cord injuries, macular degeneration, type 1 diabetes, and heart failure. However, significant hurdles remain, including immune rejection, tumorigenicity, and batch-to-batch variability. **Conclusion:** Cell therapies represent a paradigm shift from lifelong symptom management to definitive cures. Resolving biological, technical, and regulatory hurdles is imperative for the safe, standardized, and widespread clinical translation of these interventions. **Relevance for Patients:** For patients suffering from chronic, degenerative, or currently incurable conditions, stem cell therapies represent a transformative clinical paradigm. By facilitating functional tissue regeneration and targeted immunomodulation, these therapies reduce the burden of chronic pharmacotherapy and invasive procedures.

Keywords: Stem cell; Regenerative medicine; Differentiation; Degenerative diseases; Cell-based therapies

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1. Introduction

Stem cells were first functionally identified in the early 1960s through the pioneering experiments of James E. Till and Ernest A. McCulloch.[1] In their seminal studies, transplantation of bone marrow (BM) cells into lethally irradiated mice led to the formation of discrete colonies in the spleen, with colony numbers proportional to

the number of injected cells.[2] Subsequent cytological analyses demonstrated that each colony originated from a single progenitor cell capable of both proliferation and multilineage differentiation, providing the first experimental evidence for the existence of hematopoietic stem cells (HSCs).[3,4] These findings established the conceptual foundation of stem cell biology.

Stem cells are defined as undifferentiated cells characterized by two fundamental properties: long-term self-renewal and the capacity to generate differentiated progeny.[5] Self-renewal refers to the ability to undergo cell division while maintaining the undifferentiated state, whereas differentiation enables the production of specialized cell types.[6] Importantly, simple proliferative ability alone does not define a stem cell; rather, it is the regulated balance between self-renewal and lineage commitment that distinguishes stem cells from transient amplifying or progenitor cells.[7]

Based on developmental potential, stem cells are classified as totipotent, pluripotent, multipotent, or unipotent.[8] Totipotent cells, such as the zygote, can give rise to all embryonic and extraembryonic tissues. Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs), can generate derivatives of all three germ layers.[9,10] In contrast, adult (somatic) stem cells are typically multipotent and contribute to the maintenance and repair of specific tissues. For example, HSCs continuously replenish the diverse populations of blood cells throughout life, while epithelial stem cells maintain the integrity of the skin and intestinal lining.[11,12]

In adult organisms, stem cells reside within specialized microenvironments, or niches, that regulate their quiescence, activation, self-renewal, and differentiation through tightly controlled molecular and cellular signals.[13,14] Disruption of these regulatory mechanisms can lead to pathological conditions. Aberrant self-renewal and impaired differentiation are hallmarks of many malignancies, whereas defects in developmental signaling pathways contribute to congenital abnormalities.[15] Therefore, understanding the genetic and molecular networks governing stem cell fate decisions is essential for elucidating disease mechanisms.[16]

Beyond their physiological roles, stem cells have become indispensable tools in biomedical research. They provide in vitro systems to study early development, lineage specification, and gene function.[17-19] The derivation of disease-specific stem cells and the development of genetically engineered models have enabled researchers to investigate pathological processes in otherwise inaccessible cell types.[20] These approaches facilitate drug screening and the identification of potential therapeutic targets.

Clinically, HSC transplantation (HSCT) represents the most established and widely applied form of stem cell-based therapy, particularly for leukemia and other hematological disorders.[21,22] In this context, transplanted stem cells reconstitute the patient's blood and immune systems following myeloablative treatment.[23] Ongoing research explores additional regenerative applications; however, significant scientific and technical challenges remain. These include ensuring controlled differentiation, achieving functional integration, minimizing immune rejection, and preventing tumorigenicity.

Collectively, stem cell research has advanced our understanding of embryonic development, tissue homeostasis, and disease. Continued investigation into the fundamental biology of stem cells and their regulatory mechanisms is essential to translate their biological potential into safe and effective therapeutic strategies.

2. Stem cell types and sources

2.1. Biological foundations, totipotency, and pluripotent networks

Stem cells are the foundational biological units of multicellular organisms, defined by two cellular hallmarks: perpetual self-renewal and multipotency (or pluripotency)[13,24] (Figure 1).

The developmental hierarchy begins with totipotency. Following fertilization, the zygote and early blastomeres possess the absolute capacity to generate a complete organism, including extraembryonic tissues such as the placenta.[25] This state is transient and governed by maternal-effect proteins and the execution of zygotic genome activation.[26] As cleavage progresses, compaction forms the blastocyst, separating the outer trophectoderm from the inner cell mass.[27]

The inner cell mass of the human blastocyst contains pluripotent cells, which, upon derivation and long-term in vitro culture, give rise to ESC cell lines.[28] Pluripotency is biologically defined as the capacity to differentiate into all three primary germ layers: ectoderm, mesoderm, and endoderm. This state is maintained by a highly integrated core transcriptional network consisting of the octamer-binding transcription factor 4 (Oct4; *POU5F1*), the SRY-box transcription factor 2 (SOX2), and the Nanog homeobox (Nanog).[29] These master transcription factors co-occupy their own promoters to form an autoregulatory loop while simultaneously recruiting chromatin remodeling complexes, such as the polycomb repressive complex 2 (PRC2), to suppress lineage-specific differentiation genes.[30]

The in vitro maintenance of human ESCs requires highly specific extrinsic mediators. Unlike murine ESCs,

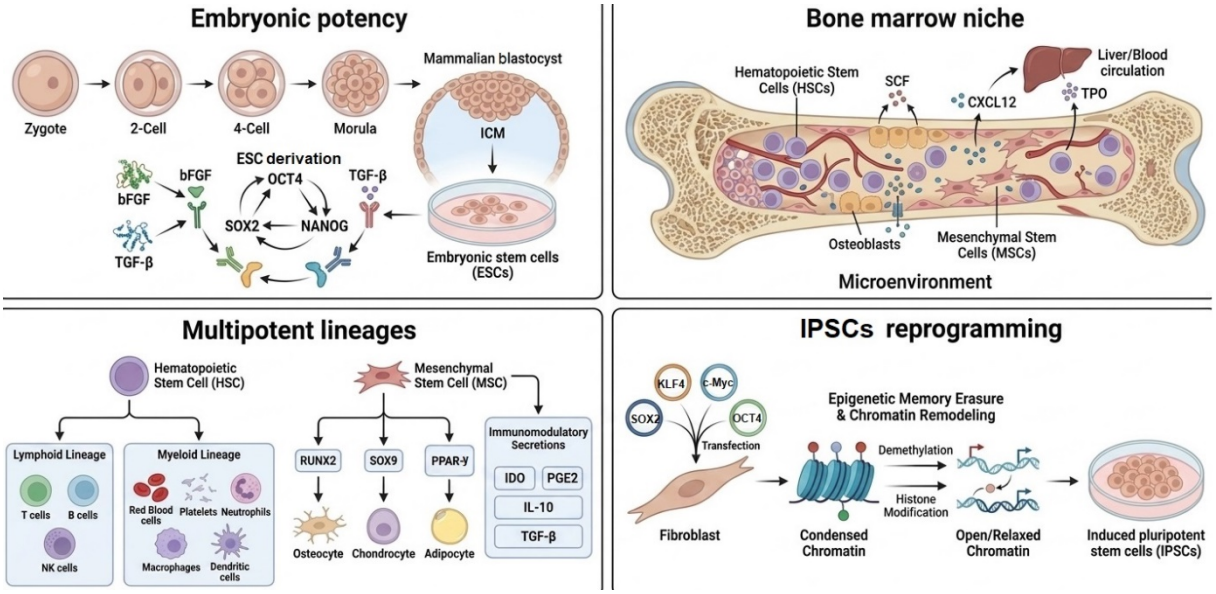

Figure 1. This infographic summarizes stem cell types and sources across development and tissue niches. Embryonic stem cells (ESCs) originate from the inner cell mass of the blastocyst and maintain pluripotency through core factors such as octamer-binding transcription factor 4 (Oct4), SRY-box transcription factor 2 (SOX2), and Nanog homeobox, and are supported by basic fibroblast growth factor (bFGF) and transforming growth factor-beta (TGF-β) signaling. Bone marrow niches contain hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), which are regulated by mediators including stem cell factor (SCF), C–X–C motif chemokine ligand 12 (CXCL12), and thrombopoietin. HSCs give rise to myeloid and lymphoid lineages, while MSCs differentiate into osteocytes, chondrocytes, and adipocytes. Somatic cells can be reprogrammed into induced pluripotent stem cells (iPSCs) using Yamanaka factors.

Abbreviations: ICM: Inner cell mass; IDO: Indoleamine 2,3-dioxygenase; IL-10: Interleukin-10; KLF4: Kruppel-like factor 4; NK: Natural killer; PGE2: Prostaglandin E2; PPARγ: Peroxisome proliferator-activated receptor gamma; TPO: Thrombopoietin.

which rely on leukemia inhibitory factor (LIF) signaling through the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway, human ESCs depend fundamentally on basic fibroblast growth factor (bFGF or FGF2) and transforming growth factor-beta (TGF-β)/activin A signaling.[31] FGF2 operates through the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathways to promote survival and proliferation, while Activin A signaling triggers the phosphorylation of SMAD family member 2 (SMAD2) and SMAD3, which translocate to the nucleus to actively sustain the transcription of Nanog.[32]

An important consideration in PSC research is that each ESC or induced pluripotent stem cell (iPSC) line represents a unique biological entity.[33] Even when derived under similar laboratory conditions, individual lines often display measurable differences in growth characteristics, genomic stability, and differentiation capacity.[34,35] These variations arise from genetic background, stochastic events during derivation, and differences in culture adaptation over time.[36] Consequently, not all PSC lines exhibit identical efficiency in producing specific cell types.

A major source of this heterogeneity lies in epigenetic regulation. PSCs maintain their identity through highly dynamic epigenetic landscapes involving DNA methylation patterns, histone modifications, and chromatin accessibility.[37,38] Small differences in these regulatory layers can influence how readily particular developmental genes become activated during differentiation. As a result, certain ESC or iPSC lines may demonstrate a bias toward specific germ-layer derivatives, such as neural, mesodermal, and endodermal lineages.[39]

In the case of iPSCs, an additional factor influencing differentiation potential is the somatic cell of origin. During reprogramming, most, but not always all, epigenetic marks associated with the original tissue are erased. Residual "epigenetic memory" can persist, meaning that iPSCs derived from blood cells, fibroblasts, or epithelial tissues may retain subtle regulatory signatures that affect their behavior.[40] This memory can sometimes facilitate differentiation toward the donor lineage while reducing efficiency for unrelated lineages.

Because of these intrinsic differences, careful characterization of each ESC or iPSC line is essential

before experimental or clinical use. Standard evaluation typically includes genomic integrity testing, pluripotency marker analysis, and functional differentiation assays to ensure reproducible and reliable results in downstream applications.

2.2. Adult multipotent lineages: Hematopoietic and mesenchymal niches

Post-embryonic tissue homeostasis relies on multipotent, lineage-restricted adult stem cells. HSCs reside in the hypoxic microenvironment of the BM. HSCs are responsible for the lifelong regeneration of the entire blood system.[41]

Hematopoietic stem cell maintenance and homing are dependent on niche-derived biochemical mediators. Stem cell factor (SCF) binds to the c-Kit (CD117) receptor tyrosine kinase on the HSC surface, activating survival pathways.[42] Furthermore, the localized retention of HSCs within the marrow is governed by the C–X–C motif chemokine ligand 12 (CXCL12; also known as stromal cell-derived factor 1 [SDF-1]), which binds to the C–X–C chemokine receptor type 4 (CXCR4) receptor on the HSC membrane. Thrombopoietin is also a critical cytokine for maintaining HSC quiescence.[43] Clinically, HSCs are identified and isolated using a distinct immunophenotype, most notably the expression of the CD34+ and CD90+ surface antigens, and the absence of lineage-specific markers Lin and CD38.[44] Upon activation, HSCs differentiate down the myeloid lineage (driven by cytokines such as erythropoietin, granulocyte colony-stimulating factor, and macrophage colony-stimulating factor) or the lymphoid lineage (driven by interleukin-7 [IL-7]).[42]

In high-impact literature, mesenchymal stem cells (MSCs) are defined by the International Society for Cell & Gene Therapy (ISCT) minimal criteria: plastic adherence, robust expression (≥95% of CD105, CD73, and CD90, absence ≤ 2%) of hematopoietic or endothelial markers (CD45, CD34, CD14/CD11b, CD79α/CD19, and human leukocyte antigen [HLA]-DR), and *in vitro* tri-lineage differentiation into osteoblasts, adipocytes, and chondroblasts.[45] Strict nomenclatural precision is essential. *Mesenchymal stromal cell* designates heterogeneous, culture-expanded populations meeting these *in vitro* parameters.[46] Conversely, the term *mesenchymal stem cell* is reserved for subsets demonstrating unequivocal *in vivo* clonal self-renewal and tissue-reconstitution capabilities.

Mesenchymal stem cells generate mesodermal lineages under the control of specific molecular mediators. Osteogenic differentiation is driven by bone morphogenetic proteins (BMPs; such as BMP-2 and BMP-7), which activate the SMAD1/5/8 pathway to upregulate Runt-related transcription factor 2 (RUNX2).[47] Chondrogenic differentiation is dependent on TGF-β,[48] which upregulates the master regulator SOX9. Adipogenic differentiation is induced in vitro by a cocktail of dexamethasone, isobutylmethylxanthine, and insulin, driving the expression of peroxisome proliferator-activated receptor gamma (PPARγ).[46,48]

Beyond their differentiation capacity, MSCs are extensively utilized for their robust paracrine and immunomodulatory functions. In inflammatory environments, MSCs are activated by pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α).[49] In response, they secrete a potent array of immunomodulatory mediators, including indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), IL-10, and TGF-β.[50,51] These secreted factors actively suppress T-cell proliferation, promote the generation of regulatory T-cells (Tregs), and shift macrophages from a pro-inflammatory M1 phenotype to a tissue-reparative M2 phenotype.[52]

2.3. Somatic cell reprogramming and induced pluripotency

The biological boundaries of cellular lineage were fundamentally disrupted in 2006 when Takahashi and Yamanaka[53] successfully derived iPSCs. This methodology involves somatic cell reprogramming, wherein terminally differentiated adult cells, such as dermal fibroblasts and peripheral blood mononuclear cells, are induced to an embryonic-like state via the ectopic expression of four specific transcription factors: Oct4, SOX2, Kruppel-like factor 4 (KLF4), and cellular myelocytomatosis oncogene (c-Myc) (the Yamanaka factors).[53]

The molecular mechanisms of this reprogramming are highly complex. c-Myc acts as a pioneering factor, binding to thousands of genomic loci to recruit histone acetyltransferases, which decoil the condensed somatic chromatin.[54] This widespread chromatin opening facilitates the binding of the core pluripotency factors, Oct4, SOX2, and KLF4, to their respective genomic targets. KLF4 specifically interacts with Oct4 and SOX2 to activate pluripotency-associated genes while actively repressing somatic-specific transcription.[55]

The reprogramming process requires an exhaustive epigenetic overhaul. Adult cells exhibit dense DNA methylation at pluripotency gene promoters, maintained by DNA methyltransferases (DNMTs).[56] During iPSC generation, this methylation must be erased to reactivate endogenous Oct4 and Nanog. The efficiency of this process is notoriously low but can be significantly enhanced by adding small-molecule biochemical mediators to the culture media, such as valproic acid (a histone deacetylase inhibitor) and 5-azacytidine (a DNMT inhibitor).[57,58]

Once fully reprogrammed, iPSCs are morphologically and transcriptionally indistinguishable from ESCs derived from the inner cell mass of blastocyst-stage embryos. They form characteristic tightly packed colonies and rely on the identical FGF2 and TGF-β cytokine pathways for in vitro maintenance.[59] Because iPSCs are generated directly from mature somatic tissues, they bypass the ethical constraints associated with embryonic tissue destruction. Furthermore, they provide a continuous, autologous cellular source, circumventing the immunological barriers to allogeneic ESC transplantation. This provides a robust, biologically accurate platform for generating patient-specific cardiomyocytes, neurons, and hepatocytes for highly detailed pharmacological screening, toxicology assays, and the precise modeling of monogenic and polygenic human pathologies in a controlled laboratory environment.

3. Stem cell-based therapy potential and underlying mechanisms

In addition to their potential to generate a diverse range of adult cell lineages, MSCs exhibit unique immunomodulatory properties that suppress immune responses in inflammatory disorders (e.g., inflammatory lung and ocular diseases).[60-62] Remarkably, MSCs can robustly regulate immune responses throughout tissue repair and provide a suitable environment for tissue replacement. A large number of studies have provided proof of concept that several trophic factors secreted by MSCs, in conjunction with cell–cell contact with immune cells, may contribute to MSC-induced immunomodulatory effects.[62,63] Accordingly, MSCs modulate both adaptive and innate immune reactions by inhibiting T- and B-cell proliferation and activation,[64,65] suppressing dendritic cell maturation[66,67] and natural killer cell cytotoxicity,[68] promoting the expansion and function of Treg cells,[69] and facilitating the polarization of pro-inflammatory M1 macrophages toward an anti-inflammatory M2 phenotype (Figure 2).[70,71] TGF-β, IL-10, hepatocyte growth factor, PGE2, IDO, and nitric oxide play central roles in the immunomodulatory functions of MSCs within the target tissue.[72,73] Moreover, to alleviate tissue ischemia, MSCs promote angiogenesis by releasing angiogenic factors, such as vascular endothelial growth factor (VEGF), FGF2, and platelet-derived growth factor, and by differentiating into vascular lineages. These mechanisms contribute to the treatment of vascular diseases by enhancing blood vessel formation and improving vascularization at ischemic tissue sites.[74-77]

The therapeutic application of ESCs and iPSCs relies primarily on terminal differentiation leading to direct functional integration, supplemented by robust vesicular paracrine signaling. The primary objective of PSC-based therapy is the structural and functional replacement of degenerative host tissue.[78] Following targeted *in vitro* differentiation, PSC-derived somatic progenitors must

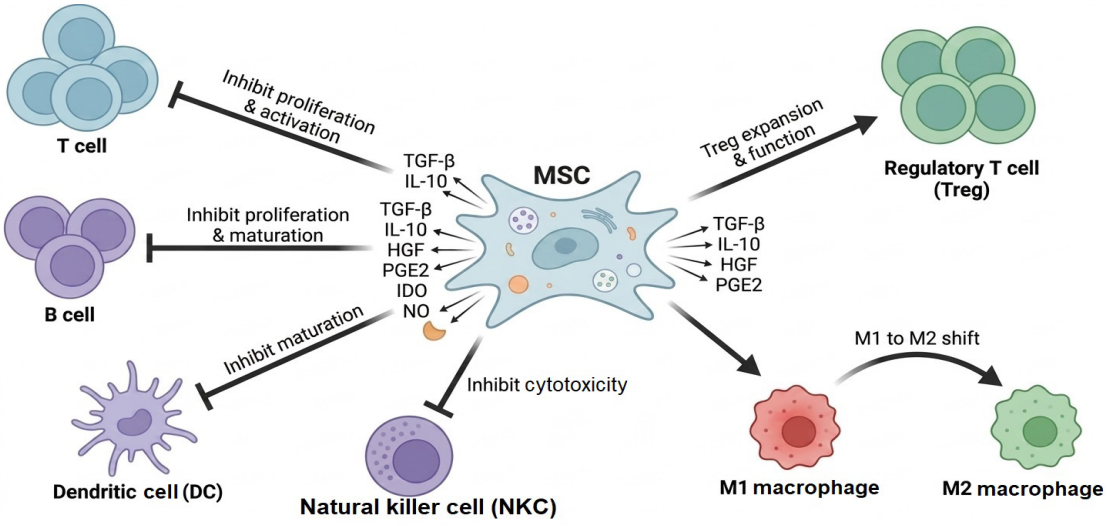

Figure 2. This infographic illustrates the therapeutic roles of mesenchymal stem cells (MSCs). MSCs modulate immune responses by shifting macrophages from an M1 to M2 phenotype, inhibiting T- and B-cell proliferation, suppressing NKC cytotoxicity, and promoting Treg expansion. They also aid ischemia rescue by secreting angiogenic and pro-survival factors that support new vascular formation and endothelial sprouting.
Abbreviations: HGF: Hepatocyte growth factor; IDO: Indoleamine 2,3-dioxygenase; IL-10: Interleukin-10; NO: Nitric oxide; PGE2: Prostaglandin E2; TGF-β: Transforming growth factor beta.

successfully engraft, achieve physiological maturation, and establish precise physical connections with existing host architecture.[79] Mechanistically, this requires highly specific cellular coupling. For example, PSC-derived cardiomyocytes must form connexin-43 gap junctions with host myocardium to achieve an electromechanical syncytium, which is essential to prevent arrhythmogenesis and restore contractile force.[80,81] Similarly, in neurodegenerative models, PSC-derived neural progenitors must undergo targeted axonal outgrowth, form structurally viable synapses, and release specific neurotransmitters to seamlessly integrate into and restore disrupted host neural circuits.[81]

Beyond direct physical replacement, PSC derivatives exert profound therapeutic effects via the localized secretion of extracellular vesicles and exosomes.[82] These nano-vesicles deliver complex, concentrated molecular cargoes, including microRNAs, long non-coding RNAs, and critical anti-apoptotic proteins, directly into the cytoplasm of stressed host cells.[83,84] This intercellular transfer fundamentally alters host gene expression profiles, actively suppresses local apoptotic cascades, and stimulates endogenous angiogenesis. Consequently, this paracrine mechanism preserves the cellular penumbra of ischemic or damaged tissues, providing substantial therapeutic benefit that operates independently of the long-term survival or integration of the graft itself[85,86] (Figure 2).

4. Clinical trials with human pluripotent stem cells in diseases

Human ESCs and iPSCs (hESCs and hiPSCs) have enormous clinical application potential. Despite all the obstacles and controversy, clinical trials are ongoing for the treatment of some diseases, such as spinal cord injury, macular retina degeneration, type 1 diabetes, and heart failure.

4.1. Spinal cord injury

Oligodendrocytes, responsible for myelinating axons and providing trophic support, are depleted following spinal cord injury. Replacing oligodendrocytes might give support to impaired axons following injury.[87] Just 12 years after the first isolation of hESCs, in a clinical trial at the Shepherd Center in Atlanta in October 2010, a patient was treated with an hESC-based cell therapy drug, hESC-derived oligodendrocyte progenitor cells (OPC1) (NCT01217008).[88,89] Only five patients were enrolled in the clinical trial for spinal cord injury. However, no unexpected serious adverse events associated with OPC1 have been reported, with a 98% follow-up of the patients over the initial 10 years of the clinical trial. Furthermore, no evidence of neurological decline, enlarging masses, additional spinal cord destruction, or syrinx formation was observed.[88,89] In another clinical trial in 2015, 25 participants with grade A or B C4–7 injuries received a single dose of OPC1 (2×10^6, 10×10^6, or 20×10^6 cells) via intraparenchymal injection into the spinal cord at the site of injury (NCT02302157).[90] At the one-year follow-up, 21 out of 22 participants (96%) in the intention-to-treat group exhibited recovery of one or more levels of neurological function on at least one side of their body, while 7 out of 22 participants (32%) demonstrated recovery of two or more levels of neurological function on at least one side. Magnetic resonance imaging scans for all participants revealed no evidence of an enlarging mass, spinal cord inflammation, spinal cord injury associated with the injection process, or masses within the ventricular system. The data on safety and neurological function warranted additional research to assess the efficacy of OPC1 in treating spinal cord injury.[90] Two additional entities have initiated spinal cord injury-related clinical trials evaluating human PSC (hPSC)-derived neural stem or precursor cells: Keio University in Japan and S.Biomedics in Korea.[87] The suggested mechanisms of action for these products involve the secretion of trophic factors at the injury site to facilitate restoration and myelination. The S.Biomedics product consists of hESC-derived neural precursor cells (PSA-NCAM+) that are administered intrathecally to patients with cervical subacute spinal cord injury. Nonetheless, data regarding safety and efficacy have not been disclosed to date.[87] The research team at Keio University, under the leadership of Hideyuki Okano, is investigating hiPSC-derived neural stem cells in cases of complete cervical and thoracic subacute spinal cord injury. As of now, four patients have received an injection of 2 million hiPSC-NSCs at 2 to 4 weeks post-injury. Although efficacy data remain unavailable, no serious adverse events have been reported.[91]

4.2. Macular degeneration of the retina

Various macular degenerative diseases result from the dysfunction and loss of the retinal pigment epithelium (RPE), a monolayer of cells that supports the overlying photoreceptors. The absence of the RPE leads to photoreceptor degeneration and subsequent vision loss.[92] Clinical investigations indicate that autologous transplantation of healthy RPE from the peripheral retina in the same eye could have beneficial outcomes.[93] Several groups have developed hPSC-derived RPE products to enhance the accessibility of therapies for patients with age-related macular degeneration (AMD) and Stargardt's macular dystrophy (SMD).[87] The first research using hESC-derived cells to treat eye disorders

started in 2011. In these investigations, a cryopreserved RPE cell suspension derived from hESC (MA09-hRPE) was administered into the subretinal region in patients with SMD (NCT01345006) or dry AMD (NCT01344993). While tiny improvements in vision were observed in these patients, the authors warned that visual acuity assessments may be unreliable for patients who have severe disease.[94-96] In this regard, the safety and efficacy of hESC-derived RPE subretinal transplantation was identified in four Asian patients: two with dry AMD and two with SMD. They were followed up for one year. There was no evidence of adverse proliferation, tumorigenicity, ectopic tissue development, or other significant safety concerns associated with the transplanted cells. In three patients, visual acuity improved by 9–19 letters, and in one patient it remained stable (+1 letter). The results suggest that cells derived from hESC could potentially serve as a safe opportunity for regenerative medicine.[97] In another clinical study, Li *et al.*[98] assessed the long-term biosafety and efficacy of hESC-derived retinal pigment epithelial (hESC-RPE) cells transplantation in early stages of SMD (NCT02749734). This study included seven patients who received a subretinal transplant of 1×10^5 hESC-RPE cells in one eye, with a follow-up period of 60 months. All seven patients exhibited either transient improvement or stabilization of visual function 1–4 months post-transplantation, with two individuals experiencing elevated intraocular pressure following the operation.[98] During the last follow-up visit, two of the seven patients showed visual function loss compared with baseline, while one patient maintained stable visual acuity. The long-term safety and tolerability of subretinal transplantation of hESC-RPE in early-stage Stargardt disease type 1(STGD1) was confirmed.[98] In 2013, the first use of hiPSC-derived RPE to target wet AMD was initiated by Masayoshi Takahashi *et al.*[99] in collaboration with the RIKEN Institute in Japan (UMIN000011929). An autologous, non-cryopreserved hiPSC-derived RPE cell sheet ($1.3 \times 3.0 \times 3.0$ mm) was extracted from a collagen matrix and administered to one eye of a patient with wet AMD without immunosuppression. Graft survival was observed in the treated eye at the fourth year, and visual acuity remained steady in that eye at both the first and fourth years without further anti-VEGF medication.[99,100] In 2015, the second study on wet/neovascular AMD by da Cruz *et al.*[101] enrolled two participants who received an RPE monolayer on a polyester membrane (NCT01691261). Enhanced visual acuity was observed at 12 months, with gains of 20 or more letters in both patients, indicating the definitive efficacy of the hPSC product. The enhanced visual acuity, however, dropped to two letters below baseline in patient 1 at five years, presumably indicating graft failure. For patient 2, the enhanced visual acuity diminished but remained nine letters over baseline after five years.[102] Sugita *et al.*[103] commenced a trial at the Kobe City Eye Hospital in Japan in 2017 to treat wet AMD (UMIN000026003). They administered cryopreserved HLA-haplotyped allogeneic iPSC-derived suspensions to five patients without immunosuppression. In these five patients, stable or improved vision was observed, with two gaining over 10 letters and three maintaining stable vision. Graft retention was established at the one-year follow-up.[103] Overall, based on the trial results, the use of hPSC products appears feasible, with no serious adverse effects from the delivered cells and no overall signs of graft rejection, even with allogeneic products.

4.3. Diabetes

Diabetes is a chronic disease that affected more than 537 million people worldwide by 2021, and this number is expected to reach 783 million by 2045.[104] It is currently estimated that 8.5% of these patients have type 1 diabetes.[105] Since 2000, the treatment protocol for patients with type 1 diabetes has begun with the transplantation of insulin-producing islet β cells.[106] However, despite promising findings, this approach is limited by the lack of deceased donors. Recent studies in this field have shown that hPSCs are a suitable source for the large-scale production of insulin-secreting cells for clinical use.[107] In 2015, the initial type 1 diabetes patient received a hESC-based pancreatic progenitor transplant.[108] This study was conducted by the regenerative medicine company ViaCyte (NCT02239354, submitted in 2014). The trial was stopped because of inconsistencies in cell survival and inadequate cell engraftment. This initial trial highlighted the need to optimize the encapsulation device.[108] In this regard, Ramzy *et al.*[109] demonstrated the safety and efficacy of PSC-derived pancreatic endoderm cells (PEC-01) to cure type 1 diabetes. PEC-01 was administered to 15 patients using a non-immunological protection macroencapsulation device. Data from these patients who received subcutaneous implantation of cell products in combination with an immunosuppressive regimen have been reported for one year of follow-up. There was no incidence of teratoma formation or severe graft side effects; implants were well tolerated. A subset of functional β cells was also observed in the injected cells. During follow-up, patients showed a 20% reduction in insulin requirements, spent 13% more time in their target blood glucose range, and maintained stable average hemoglobin A1c < 7.0%.[109] In a study by Shapiro *et al.*[110] involving 17 patients with type 1 diabetes, the ability of PEC-01 cells to regenerate and to maintain insulin production capacity when incorporated into macroencapsulation devices was examined. Twelve weeks after cell implantation, the characteristics of

endocrine cells were assessed in graft-derived cells; they expressed glucagon, insulin, or somatostatin. In addition, a mixed meal tolerance test showed that 6 of 17 patients demonstrated C-peptide responses six months after transplantation, suggesting that the implanted cells promote insulin secretion. In another study conducted in patients with type 1 diabetes (NCT03163511),[111] patients received 2–3 times more transplants than those in the two other studies.[109,110] In addition, this study used macroencapsulation devices with porous membranes to encapsulate PEC-01 cells, thereby improving survival and insulin production. Six months after transplantation, 4 of 10 recipients had detectable C-peptide (a marker of insulin secretion) in their plasma. Three of these four recipients showed improvement in glucose control at months 6 and 9.[111] Altogether, these studies raise the hope that PSC-derived PECs can serve as an alternative to pancreas or islet β-cell transplantation for the treatment of type 1 diabetes.

In a first-in-human phase I clinical trial, researchers transplanted autologous chemically induced iPSC-derived islets beneath the anterior abdominal rectus sheath of a patient with long-standing type 1 diabetes. The patient achieved insulin independence 75 days after transplantation and maintained stable glucose control throughout a one-year follow-up period.[112] Glycated hemoglobin levels remained within the normal range, while continuous glucose monitoring demonstrated a substantial increase in time spent within the target glycemic range. Importantly, no transplant-related complications, graft overgrowth, or tumor formation were observed. These findings suggest that iPSC-derived β-cell replacement therapy may offer a potentially curative treatment strategy by restoring endogenous insulin secretion and reducing dependence on exogenous insulin administration.

4.4. Heart failure

Cell replacement therapies with different cell types are presently undergoing trials in patients suffering from myocardial infarction and chronic heart failure.[87] Following a myocardial infarction, up to 1 billion cardiomyocytes may be lost and substituted with non-contractile scar tissue, a process that can subsequently lead to chronic heart failure. Several research groups are working on hPSC-derived cardiomyocytes to enhance heart contractile function.[87] Comparative studies have shown that stem cells committed to the cardiac lineage are more effective at enhancing heart function compared to those with an extra-cardiac phenotype. In 2013, Menasché *et al.*[113] conducted a case study in which they expanded undifferentiated hESCs (I6 line) and directed them toward cardiac lineage through treatment with BMP-2 and an FGF receptor inhibitor. Cells that responded to these cardio-instructive signals expressed ISL LIM homeobox 1 (ISL-1), a cardiac transcription factor, and the stage-specific embryonic antigen (SSEA-1), which were subsequently utilized for purification through immunomagnetic sorting. The ISL-1– and SSEA-1–positive cells were embedded within a fibrin scaffold, which was surgically applied to the infarct region in a 68-year-old patient with severe heart failure (New York Heart Association [NYHA] functional class III; left ventricular ejection fraction (LVEF): 26%). A coronary artery bypass was conducted simultaneously in a non-infarcted region. The patient was symptomatically improved after three months (NYHA functional Class I; LVEF: 36%), and new-onset contractility was echocardiographically noticeable in the non-revascularized region previously treated with the cell/patch. No symptoms such as arrhythmias, tumor development, and adverse effects due to immunosuppression occurred. This finding illustrates the feasibility of producing and integrating a clinically categorized population of cardiac progenitors derived from hESCs into a tissue-engineered structure. Following this study, a clinical trial (NCT02057900) involving six patients with severe ischemic left ventricular dysfunction was conducted. hESC-derived cardiovascular progenitor cells were injected into patients as a fibrin patch, and after 22.5 months, patients were followed up for safety and efficacy. Only one patient developed a severe cardiac abnormality and died after 22 months post-transplant. Symptomatic improvements were observed in the other four patients, and there has been a significant increase in wall movement in the treated cell segment.[114] The team opted to discontinue cardiomyocyte transplantation and proceed with a trial of hPSC-derived extracellular vesicles (NCT0577450),[115,116] potentially due to insufficient evidence of cell engraftment.[116,117] Miyagawa *et al.*[118] from Osaka University reported no adverse events and enhanced cardiac function in the initial patient in their trial (jRCT2053190081) one year post-transplantation following epicardial transplantation of three hiPSC-derived cardiomyocyte patches with temporary immunosuppression. In China, Help Therapeutics conducted a clinical trial in which hiPSC-derived cardiomyocyte suspensions were injected into various sites of damaged tissue, accompanied by systemic antiarrhythmic therapy (NCT03763136).[119]

Numerous factors influence the engraftment and functionality of hPSC-derived cardiomyocytes, such as maturation status, cryopreservation status, purity, product type, and delivery procedure. Successful functional implementation of transplanted cells, while simultaneously preventing arrhythmias, will be essential for advancing subsequent cardiomyocyte products.[116,117,120]

4.5. Parkinson's disease

Neurological diseases have also become major targets for iPSC-based regenerative therapies. Parkinson's disease is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra, resulting in motor dysfunction and reduced quality of life. In a phase I/II clinical trial, seven patients with Parkinson's disease underwent transplantation of allogeneic iPSC-derived dopaminergic progenitor cells into the brain.[121] Over a 24-month follow-up period, no serious treatment-related adverse events or evidence of tumor formation were observed. Neuroimaging studies demonstrated successful graft survival and dopamine production, while several patients exhibited clinically meaningful improvements in motor function scores. These findings provided the first substantial evidence that iPSC-derived neuronal replacement therapy can safely integrate into the human brain and potentially restore lost neurological function. Further analysis of the same Parkinson's disease trial investigated immune responses following transplantation. Researchers found that transplanted iPSC-derived dopaminergic neurons elicited minimal clinically significant immune reactions, even in recipients with HLA mismatches.[122] The study suggests that the relatively low expression of HLA molecules by iPSC-derived neural progenitors, combined with the immune-privileged environment of the central nervous system (CNS), contributed to successful graft survival. These findings have important implications for future allogeneic stem cell therapies, potentially reducing the need for extensive immunosuppressive regimens.[123]

Beyond direct cell replacement therapies, iPSCs have become valuable tools for drug discovery and personalized medicine. A notable example is the phase I/IIa clinical trial evaluating ropinirole in amyotrophic lateral sclerosis. This candidate drug was identified through screening studies using patient-derived iPSC motor neurons. Although the trial involved a relatively small cohort, long-term follow-up indicated reduced disease progression and prolonged progression-free survival among treated patients. This study highlights the capacity of iPSC-based disease models to accelerate therapeutic discovery and facilitate precision medicine approaches for complex neurodegenerative disorders.[124]

5. Mesenchymal stem cell therapeutic potential

Mesenchymal stem cells can be used to treat autoimmune and inflammatory disorders, mainly by modulating immune responses via soluble factors. Although MSCs exhibit immune-modulatory properties using both contact-dependent and paracrine soluble factors (e.g., growth factors, anti-inflammatory factors, chemokines, cytokines), the capacity of these cells to immigrate or home to sites of injury is of paramount importance.[125] While MSCs from diverse tissues (e.g., BM, adipose tissue, and umbilical cord) share standard ISCT criteria, they possess distinct, source-dependent biological profiles. These intrinsic variations profoundly influence their proliferation kinetics, differentiation trajectories, immunomodulatory capacities, and secretome compositions. For example, BM-MSCs typically exhibit superior osteogenic and chondrogenic differentiation potential, favoring skeletal regeneration.[126,127] Adipose tissue-MSCs yield higher initial cell quantities and secrete robust pro-angiogenic factors.[128-131] Meanwhile, neonatal umbilical cord-MSCs demonstrate accelerated proliferation, exceptional immunomodulation, and highly restricted immunogenicity.[130,131] Consequently, the optimal MSC source is not universal; tissue origin must be strategically matched to specific therapeutic objectives in regenerative medicine (Figure 3).

Mesenchymal stem cell homing to multiple sites depends on the source of these cells and on the expression of growth factor receptors, chemokine receptors, and integrins. MSCs migrate to damaged tissues in response to inflammatory mediators. For example, the CXCR4 receptor is one of the most significant chemokine receptors for SDF-1.[132] Moreover, different delivery methods are required to achieve appropriate therapeutic efficacy depending on the clinical symptoms and pathologies. Today, there are various methods for MSCs' delivery, such as intramuscular, intravenous, and intra-arterial injection.[133] Currently, various investigations have shown that after MSC transplantation in neurodegenerative disorder rodent models, neuronal regeneration, inhibition of inflammation, and clearance of accumulated toxic proteins increased.[134] MSCs can be differentiated into cardiomyocytes, endothelial cells, and vascular smooth muscle cells via various paracrine factors and can promote cardiac repair. Some studies have demonstrated that BM-MSCs in murine models can be differentiated into cardiomyocytes by 5-azacytidine, a chemical agent that inhibits DNA methylation, reflecting their potential to treat cardiac disorders.[135] Additionally, they play a fundamental role in the restoration of bone and cartilage tissues by differentiating into osteoblasts and chondrocytes, forming bone and cartilage. It has been found that MSC differentiation into osteoblasts is supported by specific transcription factors, such as RUNX2 and SP7, thereby modulating gene expression.[136] MSCs repair damaged cartilage by acting as chondroprogenitor cells to replace damaged cartilage or as regenerative cells to induce regeneration of cartilage

tissue using endogenous cells.[137] For example, evidence suggests that the use of MSCs suspended for intra-articular transplantation in the knee joints of osteoarthritis pig models increased MSC differentiation into chondrocytes and promoted collagen type 2 expression, leading to cartilage repair.[138] Clinical studies with MSCs showed their immunomodulatory potential during the COVID-19 pandemic.[139] These findings emphasize the role of MSCs in reducing inflammatory cell infiltration and lung damage, as well as improving patient recovery and survival in the early stages.[140] BM-MSC treatment has been used in several preclinical and clinical investigations for the management of chronic kidney disease. BM-MSCs have demonstrated anti-fibrotic and regenerative properties, suggesting their therapeutic potential as an alternative treatment for chronic kidney disease.[141] Considering their immunogenicity and low immunoregulatory activity, umbilical cord-MSCs are particularly attractive for therapeutic use. These cells are used to treat hematological conditions such as thrombocytopenia, aplastic anemia, and graft-versus-host disease by inhibiting tumor cell growth, alleviating complications after HSCT, and promoting hematopoiesis.[142] MSCs appear promising for treating premature ovarian failure (POF) based on preliminary findings from preclinical, clinical, and laboratory-based studies. Numerous studies have demonstrated that because human MSCs are extensively accessible and differentiate into most tissues, they provide remarkable clinical transformation and application potential in POF patients to fundamentally restore ovarian function. MSCs acquired through various procedures and sources had the same therapeutic effects in restoring reproductive function in POF patients.[143] In polycystic ovary syndrome (PCOS), MSCs increase the number of eggs and corpora lutea and decrease the number of ectopic cystic follicles, according to preclinical and clinical research. In women with PCOS, they also lessen granulosa cell inflammation. However, more thorough research is required due to the paucity of information on the use of MSCs in PCOS treatment[144] (Figure 3). A summary of MSCs application in regenerative medicine are provided in Table 1.

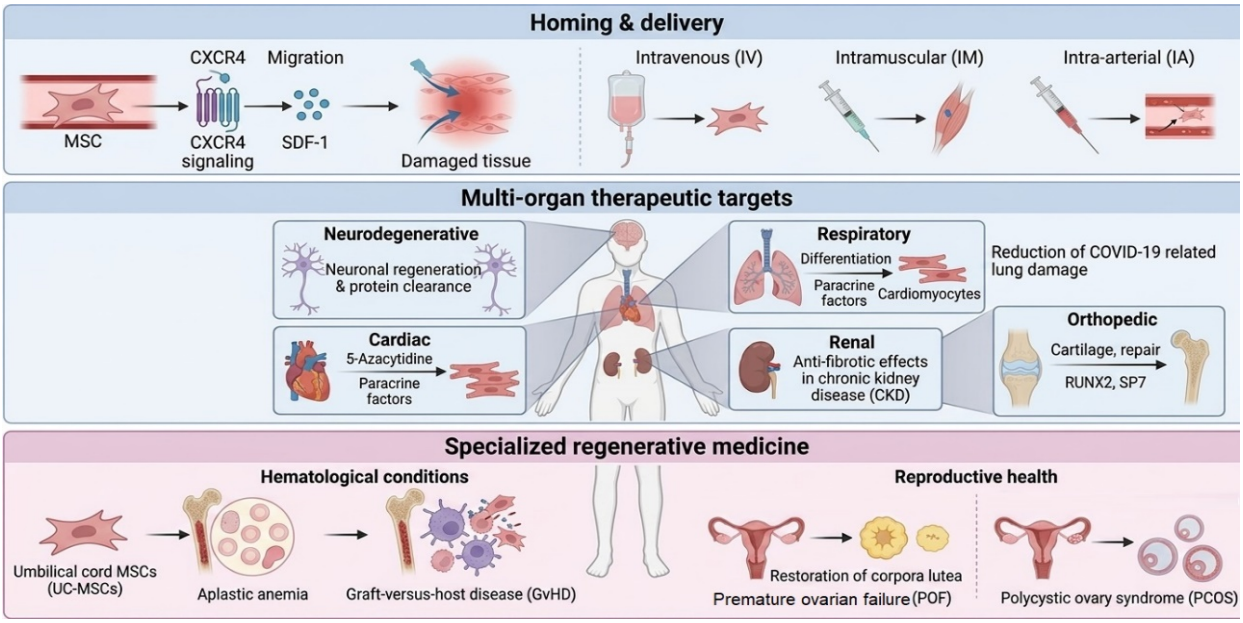

Figure 3. This infographic details the clinical deployment and therapeutic targets of mesenchymal stem cells (MSCs). The homing and delivery section illustrates how MSCs migrate to damaged tissue via the C–X–C chemokine receptor type 4 (CXCR4)/stromal cell-derived factor 1 (SDF-1) signaling axis, highlighting intravenous, intramuscular, and intra-arterial administration routes. The multi-organ therapeutic targets section showcases MSC applications in neurodegenerative disorders (neuronal regeneration), cardiac repair (facilitated by 5-azacytidine), respiratory conditions (COVID-19 lung damage), renal fibrosis in chronic kidney disease, and orthopedic cartilage repair (driven by Runt-related transcription factor 2 [RUNX2]/SP7). Finally, specialized regenerative medicine highlights umbilical cord-MSCs for hematological conditions such as graft-versus-host disease and reproductive health issues, including premature ovarian failure and polycystic ovary syndrome.

Table 1. Mesenchymal stem cell-based therapy in regenerative medicine

Condition	Model	Main consequences	Reference
OA	Sprague-Dawley rat	Inhibition of OA progression	145
Emphysema	Papain-induced rat	Induction of protection against pulmonary emphysema by increasing VEGF-A	146
OA	Mouse	Pain reduction and cartilage damage	147
RA	Mouse	Inhibition of inflammation by targeting TH17 differentiation	148
ALS	*SOD1G93A* mice	Neuroprotection and motor functions	149
ALS	*SOD1G93A* mice	Induction of neuroprotection by release of neurotrophins	150
OA	Beagle dogs	OA rescue	151
OA	Rabbit	Induction of cartilage protection by up-regulation of expression of growth factors	152
RA	Mouse	Modification of migration and invasion of FLS	153
PD	MPTP-induced mice	Alleviation of dopaminergic neuron damage	154
PD	MPTP-induced mice	Diminishing of the blood–brain barrier damage and neuroinflammation	155
RA	Mouse	Decreased inflammation	156
OA	Mouse	Attenuation of chondrocytes apoptosis	157
RA	Rat	Attenuation of expression of RANKL	158
RA	Rat	Inhibition of the proliferation of T lymphocytes, and activating Tregs	159
AD	Tg2576 mice	Improvement of memory impairment	160
AD	Tg2576 mice	Improved cognitive function by diminishing oxidative stress	161
OA	Mouse	Reduced cartilage damage	162
OA	Horse	No positive effect	163
RA	Mouse	Decreased disease progression	164
PF	Silica-induced rat	Inhibited inflammation and reduced caspase-3 protein expression	165
BPD	Hyperoxia-induced rat	Inhibition of fibrosis and pulmonary vascular remodeling	166
RA	Mouse	Inhibition of inflammation	167
OA	Fischer 344 rat	Moderation of MMPs expression	168
OA	Rabbit	Induction of cartilage tissue regeneration	169
OA	New Zealand rabbit	Reduction of inflammatory cytokine levels	170
Asthma	Ovalbumin-induced mice	Attenuation of numbers of goblet cells, the thickness of the smooth muscle layer	171
ALI/ARDS	Bleomycin-induced rat	Promotion of vascular permeability, decrease in the rates of proinflammatory cytokines	172
Asthma	Ovalbumin-induced mice	Improved lung function	173
Emphysema	CS-induced rat	Inhibition of emphysema development	174
OA	Horse	Diminution of inflammation	175
OA	Rat	Reduced pain	176
RA	Mouse	Induction of T-cell apoptosis	177
MS	EAE rat	Induction of myelin regeneration	178
MS	EAE mice	Suppression of TNF-α and MPO expression	179
MS	EAE mice	Reduction of T-cell activation and promotion of remyelination	180

Abbreviations: AD: Alzheimer's disease; ALI: Acute lung injury; ALS: Amyotrophic lateral sclerosis; ARDS: Acute respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; CS: Cigarette smoke; EAE: Experimental autoimmune encephalomyelitis; FLS: Fibroblast-like synoviocytes; MMP: Matrix metalloproteinase; MPO: Myeloperoxidase; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS: Multiple sclerosis; OA: Osteoarthritis; PD: Parkinson's disease; PF: Pulmonary fibrosis; RA: Rheumatoid arthritis; RANKL: Receptor activator of nuclear factor κB ligand; TH17: T helper 17; TNF-α: Tumor necrosis factor-α; Tregs: Regulatory T cells; VEGF-A: Vascular endothelial growth factor A.

As shown in Figure 3, MSCs may exert beneficial effects that influence many aspects of neuroregeneration and neuroprotection.[181] MSCs play a role in neurogenesis, the generation of new neurons, which is necessary to sustain cognitive and motor functions, particularly after injury, and during neurodegenerative diseases. Likewise, MSCs play a role in synaptogenesis, the generation of synaptic connections between neurons, which is required to restore neural communication and recover some function in the injured CNS.[182] Another important contribution of MSCs is their ability to promote angiogenesis, the formation of new blood vessels, which allows adequate oxygen and nutrients to be supplied to injured or ischemic tissue and creates a suitable microenvironment for tissue repair.[183,184] MSCs also support the survival and differentiation of oligodendrocytes, thereby maintaining myelin sheaths and healthy neuronal axons in the CNS.[185] Furthermore, MSCs play an important role in remyelination, the restoration of new myelin sheaths around demyelinated axons, common in demyelinating disorders such as multiple sclerosis.[186] Remyelination restores neural conduction and protects axons from further degeneration. In addition to encouraging regenerative processes, MSCs also have strong immunomodulatory and anti-inflammatory effects.[187-189] They exert inhibitory effects on microglial activation, the resident immune cells of the CNS. When activated, microglia can release pro-inflammatory cytokines, further damaging the CNS.[190-192] Additionally, MSCs curb astrogliosis, the excessive proliferation and/or activation of astrocytes, which can lead to the formation of glial scar tissue and disrupt neuronal regeneration and repair.[193,194] By modulating reactive gliosis, MSCs can help maintain the structural and functional integrity of the CNS. Another essential role of MSCs is the reduction of apoptosis (programmed cell death) in neural cell types.[195] By expressing and secreting neurotrophic factors and anti-apoptotic factors,[196-198] MSCs enhance neuronal survival in the face of injury, such as stroke, trauma, and neurodegenerative disease. These functions establish the therapeutic potential of MSCs in neurological disorders. The ability to modulate immune-inflammatory responses, facilitate tissue repair, replace damaged/lost cells, and promote functional recovery constitutes a promising option for CNS regeneration (Figure 4).

6. Clinical translation and regulatory success of mesenchymal stem cell therapies

One of the earliest successes of MSC-based therapy was in the treatment of steroid-refractory acute graft-versus-host disease. TEMCELL HS Inj., an allogeneic BM-derived MSC product, became the first MSC-based therapy approved in Japan. Clinical studies demonstrated overall response rates exceeding 60%, with significant reductions in inflammatory manifestations affecting the skin, liver, and gastrointestinal tract.[199] Importantly, treatment was associated with improved survival outcomes in patients who had failed conventional immunosuppressive therapies, establishing MSCs as effective immune-regulating agents in severe graft-versus-host disease.

A major regulatory milestone was achieved with Ryoncil (remestemcel-L), which became the first MSC product approved by the United States Food and Drug Administration for pediatric steroid-refractory acute graft-versus-host disease.[200] Clinical investigations reported overall response rates approaching 70% at day 28, with responders showing significantly improved long-term survival compared with non-responders. The therapy demonstrated a favorable safety profile and provided a much-needed treatment option for children with limited therapeutic alternatives.

Mesenchymal stem cells have also shown remarkable potential in orthopedic regenerative medicine. Cartistem, an allogeneic umbilical cord blood-derived MSC product approved in South Korea, is used for cartilage regeneration in patients with knee osteoarthritis.[201] Clinical studies demonstrated significant improvements in pain scores, joint function, and cartilage quality as assessed by magnetic resonance imaging and arthroscopic evaluation. Long-term follow-up extending beyond five years revealed durable cartilage repair and sustained clinical benefits, supporting the regenerative capabilities of MSCs in musculoskeletal disorders.[201] A phase II randomized clinical trial evaluated 60 knee osteoarthritis patients treated with either PRGF® alone or autologous BM-MSCs plus PRGF®.[202] Over a 12-month follow-up, both treatments were safe with no adverse effects. While neither group showed structural joint changes on imaging, the BM-MSC plus PRGF® group demonstrated significant pain reduction on the visual analog scale (VAS). Although Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score improvements were similar and lacked inter-group statistical significance, only patients receiving BM-MSCs plus PRGF® met Osteoarthritis Research Society International (OARSI) responder criteria. This combination is a viable, safe therapeutic option, warranting future phase III clinical trials.[202]

In gastroenterology, Alofisel (darvadstrocel) became the first MSC-based product approved in Europe for the treatment of complex perianal fistulas in Crohn's disease.[203] In the pivotal ADMIRE-CD trial, combined remission rates were significantly higher in MSC-treated patients than in control groups.[204] Long-term follow-up studies demonstrated sustained fistula closure and reduced disease

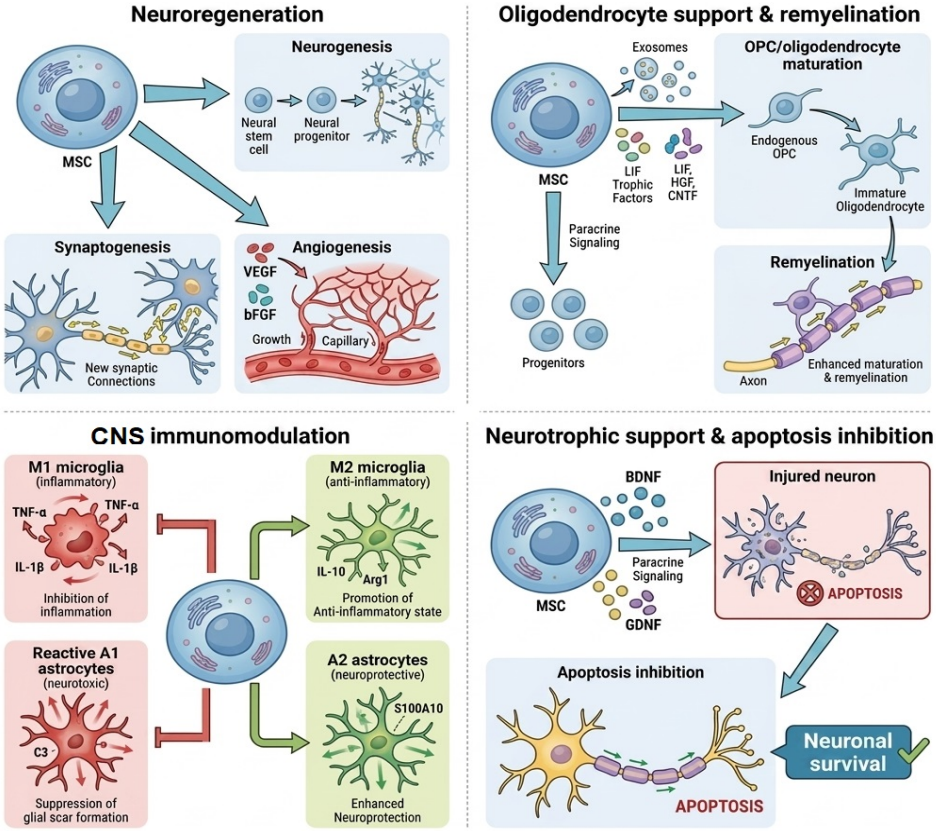

Figure 4. This infographic delineates the diverse mechanisms through which mesenchymal stem cells (MSCs) promote neuroregeneration and neuroprotection. MSCs facilitate neurogenesis and synaptogenesis while supporting angiogenesis by secreting VEGF and bFGF. They further aid structural repair by promoting the differentiation of oligodendrocyte progenitors into mature oligodendrocytes, thereby remyelinating damaged axons. In a protective capacity, MSCs inhibit the activation of pro-inflammatory M1 microglia and A1 astrocytes, thereby reducing astrogliosis and glial scar formation. Additionally, MSCs secrete neurotrophic factors, such as BDNF and GDNF, which directly counteract neuronal stress and inhibit apoptosis.
Abbreviations: Arg1: Arginase 1; BDNF: Brain-derived neurotrophic factor; bFGF: Basic fibroblast growth factor; CNS: Central nervous system; CNTF: Ciliary neurotrophic factor; GDNF: Glial cell line-derived neurotrophic factor; HGF: Hepatocyte growth factor; IL-1β: Interleukin-1β; LIF: Leukemia inhibitory factor; OPC: Oligodendrocyte precursor cell; TNF-α: Tumor necrosis factor-α; VEGF: Vascular endothelial growth factor.

recurrence, highlighting the ability of MSCs to modulate chronic intestinal inflammation and promote tissue healing.

Beyond approved indications, MSCs have shown encouraging results in cardiovascular diseases. Clinical trials involving patients with ischemic cardiomyopathy and heart failure have reported improvements in LVEF, reduced scar formation, and enhanced quality of life following MSC administration.[205,206] A recent randomized, double-blind MSC-HF trial evaluated intramyocardial MSC injections versus a placebo in 60 patients with severe ischemic heart failure.[206] During the 12-month follow-up, the MSC cohort demonstrated significant, dose-dependent improvements in the primary efficacy endpoint of left ventricular end-systolic volume. These findings were accompanied by concurrent increases in LVEF, stroke volume, and viable myocardial mass, alongside a reduction in myocardial scar burden and enhanced health-related quality of life. The intervention was well-tolerated, with no treatment-related adverse events reported. Longitudinal analysis at four years revealed a statistically significant reduction in hospital admissions for angina pectoris among MSC recipients, though overall survival rates remained comparable between the study arms.[206]

Mesenchymal stem cell-based therapy has also been extensively investigated for the treatment of autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. Several early-phase clinical trials reported reductions in disease activity scores, decreased inflammatory cytokine production, and improved clinical symptoms, supporting the immunoregulatory capacity of MSCs.[207] During the

COVID-19 pandemic, MSCs were also evaluated for severe acute respiratory distress syndrome (ARDS), with preliminary studies suggesting reductions in inflammatory markers, improved oxygenation, and potential survival benefits.[208] In a recent study, 11 mechanically ventilated patients with COVID-19-induced ARDS received intravenous umbilical cord or placental MSCs. Six survivors exhibited rapid respiratory improvement, significantly attenuated inflammatory cytokines (TNF-α, IL-8, C-reactive protein), and substantial 60-day radiological lung recovery.[209] Conversely, five patients succumbed to severe complications, including multi-organ failure and sepsis.

Other studies assessed the safety and efficacy of BM-MSCs in newly diagnosed type 1 diabetes patients. For example, a recent trial investigated intravenous autologous BM-MSCs in 21 newly diagnosed type 1 diabetes patients, finding the therapy safe and capable of reducing hypoglycemic episodes.[210] Over a one-year follow-up, MSCs improved HbA1c and C-peptide levels and shifted immune profiles toward an anti-inflammatory state. Critically, claiming broad efficacy is premature. The study suffers from a severely limited sample size (n = 21) and a short one-year follow-up, insufficient to evaluate long-term durability in lifelong autoimmune diseases. Furthermore, the conclusion abruptly targets children, although pediatric demographics were omitted in the methods.[210]

Collectively, the clinical success of TEMCELL, Ryoncil, Cartistem, and Alofisel, together with promising outcomes in cardiovascular, autoimmune, and pulmonary diseases, has established MSCs as the most mature and commercially successful stem cell therapy platform. These achievements provide critical clinical and regulatory frameworks that are now guiding the development and translation of next-generation regenerative therapies, including those derived from iPSCs.[211]

7. Hematopoietic stem cell therapeutic potential

The current potential separation of extensive diversity of somatically derived stem cells has confirmed the idea that homeostatic conservation of most tissues and organs is regulated by the tissue-specific stem and progenitor cells and has sparked interest in the use of these cells in approaches intended at restoring or replacing damaged, diseased, or genetically deficient tissues and organs.[212] HSCs, multipotent adult tissue stem cells with the capacity to differentiate into mature blood cell lineages, are derived from peripheral blood, BM, and umbilical cord blood. These cells are currently utilized in clinical hematology to address a range of malignant, autoimmune, and inherited metabolic disorders.[213-215] The gold standard for many blood disorders is HSCT.[216] Additionally, HSCT is used to reconstitute hematopoiesis after high-dose chemotherapy for the treatment of solid tumors.[217] Undoubtedly, there is a tight association between hematopoietic reconstitution after BM ablation and the movement and homing of stem cells to the hematopoietic microenvironment in the BM niches of the recipient.[217]

Despite opposing conditions in the host BM niches, the transplanted HSCs generate sufficient progenitors to restore the host hematopoietic system with mature cells. In 2006, the Center for International Blood and Marrow Transplant Research (IBMTR) collected data from about 400 worldwide transplant centers and showed that hematological malignancies are the most common indications for allogeneic HSCT. Accordingly, acute myeloid leukemia accounts for 33% of allogeneic HSCTs, acute lymphoblastic leukemia 16%, chronic myeloid leukemia 6%, other leukemias and preleukemia 18%, Hodgkin lymphoma and non-Hodgkin lymphoma 12%, and multiple myeloma 3%.[218]

Furthermore, over the past three decades, HSCT has been developed as a specific treatment option for severe autoimmune diseases, such as multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, arthritis, and Crohn's disease.[219] The initial idea of using HSCT to treat severe autoimmune diseases arose from observations that HSCT in animal models and case reports led to long-term improvement in these conditions.[220] In this approach, granulocyte-colony stimulating factor is used to mobilize HSCs into the peripheral blood. The graft is then collected via leukapheresis and stored using cryopreservation techniques. Ultimately, this autologous HSCT is used to restore rapid and sustained hematopoiesis. After the elimination of lymphocytes (including self-reactive lymphocytes) through high-dose chemotherapy, autologous HSCT is usually used to achieve rapid and sustained hematopoietic recovery.[221]

Today, there is evidence supporting the hypothesis that HSCT can be used to treat various immunological disorders. For example, in the context of gene delivery using HSCs, Aiuti *et al.*[222] conducted a clinical trial to investigate the effects of hematopoietic stem/progenitor cell (HSPC) transplants in Wiskott–Aldrich syndrome (WAS), an inherited immunodeficiency caused by mutations in the gene encoding WAS protein (WASP). They used a lentiviral vector encoding functional WASP to genetically modify HSPCs from three WAS patients, and reinfused the cells after an abridged-intensity conditioning regimen. Based on observations, all three

participants demonstrated permanent engraftment of WASP-expressing cells and restoration in platelet counts, immune activity, and clinical scores. Importantly, lentiviral gene therapy showed no integrations near oncogenes and abnormal clonal expansion during two years of follow-up. These findings provide evidence for the safety and efficacy of genetically modified HSPCs for treating WAS. Similarly, another clinical trial conducted between April 20, 2010, and Feb 26, 2015, in nine participants with WAS revealed that engraftment of genetically modified HSPCs was effective and continued in all patients. Interestingly, the fraction of WASP-positive lymphocytes increased from a median of 3.9% before intervention to 66.7%, and WASP-positive platelets increased from 19.1% to 76.6% at one year after transplantation. Though severe untoward events, such as pyrexia and device-related infections, occurred in six participants during follow-up, no adverse responses to the investigational drug product and no atypical clonal expansion or leukemia were described upon transplantation. These results signify that gene therapy delivers an appreciated treatment choice for patients with severe WAS, predominantly for those who do not have an appropriate HSPC donor accessible. Additionally, gene therapy using HPCs has been hypothesized to treat patients with X-linked adrenoleukodystrophy (ALD), caused by mutations in *ABCD1*, which encodes ALD protein.[223] In a phase II–III safety and efficacy trial, the 17 participants were reinfused with autologous HSPCs transduced with a lentiviral vector. According to the results, all participants had gene-marked cells after engraftment, without any preferential integration near recognized oncogenes or clonal outgrowth. In addition to the observation of the measurable level of ALD protein, no treatment-associated death or graft-versus-host disease had been reported. In summary, these findings indicate that lentiviral-D gene therapy may be a safe and effective option for allogeneic stem-cell transplantation in patients with X-linked ALD.[223] A phase I/II trial involving six children with β^0 or severe β^+ mutations showed that autologous HSCs genetically modified to express β-globin may represent a potential therapeutic option for β-thalassemia.[224] Considering consequences, swift hematopoietic restoration with polyclonal multilineage engraftment of vector-marked cells was achieved, with a median of 37.5% in hematopoietic progenitors and a vector copy number per cell of 0.58 in erythroid precursors at 12 months, without clonal dominance.[224] A summary of HSC-based gene therapy is provided in Table 2.

Among stem cell types, HSCs and the various progenitors derived from their differentiation have diverse applications in the treatment of non-hematological diseases and can also be used in regenerative medicine as a promising cell source for the treatment of pathophysiological conditions.[214] Previous studies have reported the capacity of human HSCs to differentiate into liver, skin, and intestinal cells.[225] In this regard, several studies have used HSCs to treat liver diseases in humans and have shown their positive role in improving liver function and regeneration.[226-230]

Table 2. An overview of recent preclinical and clinical studies of HSC-based gene therapy

Diseases	Gene	Main results	Reference
MPS IIIA	SGSH	Amelioration of MPS IIIA behavior, GM2 ganglioside, and neuroinflammation in MPS IIIA rodent models upon HSCT	231
Hemophilia A	F8	Acquisition of sufficient *F8* expression after transplantation in hemophilia A rodent models upon HSCT	232
LSD	CTNS	Cystinosin transferring from CTNS-expressing cells to CTNS-deficient adjacent cells in LSD rodent models upon HSCT	233
MPS II	IDS	Alleviation of the secondary accumulation of autophagic substrates (e.g., p62 and ubiquitin-protein conjugates) in the cerebrum of MPS II rodent models upon HSCT	234
CLAD	ITGB2	Correction of the CLAD phenotype in dog models upon HSCT	235
IMO	TCIRG1	Alleviation of osteopetrosis in IMO rodent models	236
ALD	ABCD1	Verification of the safety and possible efficacy of HSCT in patients with early-stage cerebral ALD	223
MLD	*ARSA*	Showing extensive and stable *ARSA* gene replacement, causing enzyme expression throughout hematopoietic lineages and in cerebrospinal fluid of patients with MLD	237

(*Cont'd...*)

Table 2. (*Continued*)

Diseases	Gene	Main results	Reference
WAS	*WAS*	Verification of the safety of HSCT in patients with WAS	222
SCID-X1	*IL2RG*	Showing the selective expansion of gene-marked T cells, natural killer cells, and B cells associated with sustained restoration of humoral responses to immunization and clinical improvement at 2 to 3 years after HSCT in patients with SCID-X1	238
β-thalassemia	*HBB*	Showing rapid hematopoietic recovery with polyclonal multilineage engraftment of vector-marked cells in erythroid precursors in patients with β-thalassemia	224
WAS	WAS	Verification of the safety and efficacy of HSCT in patients with WAS	239
β-thalassemia	*HBB*	Reduction or elimination of the need for long-term red-cell transfusions without serious adverse events in patients with β-thalassemia	240
FA	*FANCA*	Showing the acquired resistance of hematopoietic progenitors and T lymphocytes to DNA cross-linking agents along with the suppression of the arrest of bone marrow failure in patients with FA	241
MLD	*ARSA*	Verification of the safety and efficacy of HSCT in patients with MLD	242
SCD	*HBB*	Verification of the safety of HSCT in patients with SCID	243
ALD	*ABCD1*	Verification of the safety of HSCT along with the reduction of cerebral demyelination in patients with ALD	244
WAS	*WAS*	Showing that hematopoietic stem cell transplantation for WAS is feasible and effective, but the use of γ-retroviral vectors is associated with a substantial risk of leukemogenesis in patients with WAS	245
SCID	*ADA*	Verification of the safety and efficacy of HSCT in patients with SCID	246

Abbreviations: ALD: Adrenoleukodystrophy; ARSA: Arylsulfatase A; CLAD: Canine leukocyte adhesion deficiency; CTNS: Cysteine transporter; FA: Fanconi anemia; FANCA: FA complementation group A; HbS: Hemoglobin S; HSCT: Hematopoietic stem-cell transplantation; IDS: Iduronate 2-sulfatase; IMO: Infantile malignant osteopetrosis; LSD: Lysosomal storage disease; MLD: Metachromatic leukodystrophy; MPS II: Mucopolysaccharidosis II; MPS IIIA: Mucopolysaccharidosis IIIA; SCD: Sickle cell disease; SCID-X1: X-linked severe combined immunodeficiency; SGSH: N-sulfoglucosamine sulfohydrolase; TCIRG1: T-cell immune regulator 1; WAS: Wiskott–Aldrich syndrome.

8. Challenges

Pluripotent stem cell- and MSC-based therapies have emerged as two of the most promising approaches in regenerative medicine. While both platforms offer significant therapeutic potential, they face distinct scientific, manufacturing, regulatory, and clinical challenges that must be addressed to achieve widespread clinical implementation. At the same time, recent technological advances are creating unprecedented opportunities to overcome these barriers and expand the therapeutic scope of stem cell-based interventions.

Among PSCs, including ESCs and iPSCs, one of the primary challenges is immune rejection following transplantation.[247,248] Although autologous iPSC-derived products theoretically eliminate immunological incompatibility, individualized manufacturing is time-consuming, expensive, and difficult to scale.[249] To address this limitation, the Center for iPS Cell Research and Application (CiRA) at Kyoto University has established an HLA-homozygous iPSC stock project designed to generate allogeneic iPSC lines that are immunologically compatible with a substantial proportion of the population.[250] This strategy has the potential to reduce immune rejection while enabling the production of standardized, off-the-shelf cell therapies. Early clinical applications, including Parkinson's disease and corneal regeneration trials, have demonstrated the feasibility of this approach and represent an important step toward large-scale implementation of iPSC-based regenerative medicine.[121]

Another major challenge for PSC-derived therapies is the risk of teratoma formation arising from residual undifferentiated PSCs.[251] Even small numbers of remaining PSCs may, in theory, generate teratomas following transplantation. Consequently, stringent quality-control measures, purification strategies, and safety testing are required before clinical use.[252] Advances in cell sorting,

suicide gene systems, and lineage-specific differentiation protocols have substantially reduced these risks, but long-term surveillance remains essential. In addition, PSC manufacturing requires highly standardized differentiation procedures to ensure reproducible cell identity, functionality, and safety across production batches.[253]

Gene-editing technologies are creating new opportunities to overcome immunological barriers in PSC therapies. Several biotechnology companies, including Sana Biotechnology, are developing hypoimmune stem-cell platforms using clustered regularly interspaced short palindromic repeats (CRISPR)-based genome engineering.[254,255] By modifying key immune recognition pathways, these engineered cells can evade detection by host T cells and natural killer cells, potentially enabling universal donor cell products.[256] Such approaches may eliminate the need for long-term immunosuppression and significantly broaden the clinical applicability of allogeneic PSC-derived therapies.

In contrast to PSC-derived products, MSC-based therapies have already achieved substantial clinical success, with approved products, such as Cartistem, Alofisel, TEMCELL, and Ryoncil, demonstrating efficacy in orthopedic, inflammatory, and immune-mediated disorders. MSCs possess intrinsic immunomodulatory properties and exhibit relatively low immunogenicity, making them attractive candidates for allogeneic transplantation.[257] Furthermore, their favorable safety profile and limited tumorigenic potential have facilitated rapid clinical translation.[258]

Despite these advantages, MSC therapies face critical challenges. One of the most significant is batch-to-batch variability during manufacturing.[259] MSCs derived from different donors, tissues, or culture conditions often exhibit substantial heterogeneity in proliferation capacity, differentiation potential, secretory profiles, and therapeutic efficacy.[260,261] Such variability complicates quality control and may contribute to inconsistent clinical outcomes across studies. Establishing standardized manufacturing protocols and potency assays remains a critical priority for the field.

Scalability also represents a major obstacle for MSC-based therapies.[262] Large-scale expansion can induce cellular senescence, phenotypic drift, and loss of therapeutic function, limiting the production of consistent, high-quality cell products.[263] Furthermore, the mechanisms underlying MSC efficacy remain incompletely understood, with increasing evidence suggesting that paracrine signaling and extracellular vesicles may contribute more significantly than direct tissue engraftment.[262,264] This has prompted growing interest in cell-free MSC-derived exosome therapies as potentially safer and more scalable alternatives.[265]

Overall, PSC- and MSC-based therapies present complementary strengths and challenges. PSCs offer virtually unlimited self-renewal and differentiation capacity, making them particularly attractive for cell-replacement therapies, whereas MSCs currently possess a more established clinical track record and a favorable safety profile. Future advances in immune engineering, gene editing, manufacturing standardization, and large-scale bioprocessing are expected to further accelerate the clinical translation of both platforms, ultimately expanding the therapeutic landscape of regenerative medicine.

9. Conclusion

Degenerative diseases and other life-threatening diseases establish an incredible social load due to their overwhelming nature, cost, and lack of effective treatments. Presently, cellular replacement therapies hold marked promise for the treatment of a wide spectrum of disorders, and several studies to date have verified the efficacy of the stem cell strategy in degenerative and inflammatory diseases through the release of trophic factors, particularly growth factors. However, before stem cell technology is applied in clinics and stem cell-based therapies are translated from the bench to the bedside, resolving various challenges is of paramount importance. Accordingly, the pathophysiology of each disease is specific and therefore requires careful attention. Besides, the cost, safety, manpower requirements, and post-transplant monitoring are other pivotal subjects. With continued investments in research and technological innovations, stem cell therapies have the potential to revolutionize modern medicine. They could ultimately shift the paradigm from symptom management to curative interventions, paving the way for more effective and personalized treatments. Overall, we suggest that stem cell technology can yield favorable therapeutic outcomes if more resources and attention are devoted to this context.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not applicable.

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