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Stem cell revolution: bridging the gap between research and clinical application

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Abstract

Stem cells are characterized by their capacity for self-renewal and their potential for multi-directional differentiation, enabling them to develop into various functional tissues and organs under specific conditions. Their applications hold considerable promise, and the market for stem cell products is progressively expanding. Internationally, several stem cell products have received approval for market release; however, in China, the field remains largely undeveloped, presenting substantial opportunities for growth. Recent years have witnessed significant advancements in stem cell research, driven by improvements in national policies, regulatory frameworks, and ongoing technological innovations. This progress has resulted in notable breakthroughs in basic science, as well as substantial advancements in clinical trials and industrial applications. Compared to previous decades, stem cell therapies in China have experienced remarkable progress, with numerous companies advancing to the clinical research phase, indicating a robust overall development trajectory. Nonetheless, the considerable variability in the sources, types, and preparation processes of stem cell products contributes to the complexity of their therapeutic mechanisms and in vivo activities, which are more intricate than those of traditional pharmaceuticals. Consequently, stem cell therapies encounter several challenges in drug development, including issues related to safety, induction efficiency, the exploration of clinical translation processes, and elevated research and development costs, all of which may hinder the advancement of stem cell therapies. Nevertheless, numerous companies and research institutions are actively engaged in promoting progress within the stem cell domain. It is anticipated that, as the stem cell sector continues to evolve, these challenges will be addressed, ultimately serving as a crucial catalyst for meeting various unmet clinical needs and effecting transformative changes in human healthcare and other sectors.

Keywords Stem cells, Therapy, Clinical application, Development

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Introduction

Stem cell definition and classification

Stem cells (SC) are a type of cell group with self-replication and multi-directional differentiation potential [1]. Under certain conditions, it can differentiate into various functional cells to form different tissues and organs of the human body, which can be classified according to their development stage and differentiation potential. According to their developmental stage, stem cells can be divided into embryonic stem cells (ESCs) and adult stem cells (ASCs) [2]. According to the development potential of stem cells, they can be divided into totipotent stem cells (TSC), pluripotent stem cells (PSC), and unipotent stem cells (USC) [3]. Among them, induced pluripotent stem cells (iPSCs) refer to pluripotent stem cells generated by reprogramming fully differentiated somatic cells (e.g., adult skin fibroblasts, peripheral blood cells, or dental pulp cells) using viral (e.g., retroviruses, lentiviruses) or non-viral (e.g., episomal vectors, mRNA) carrier technologies. After reprogramming, these cells regain the capacity for self-renewal and can differentiate into almost all types of cells derived from the three germ layers (ectoderm, mesoderm, endoderm), similar to embryonic stem cells [4]. In contrast, published literature confirms Very Small Embryonic-Like Stem Cells (VSELs) are a unique subset of postnatal stem cells with in vivo pluripotency—a trait that fundamentally distinguishes them from other adult stem cells (Table 1) [5]. VSELs are not "adult stem cells"—they are a distinct subset of in vivo pluripotent stem cells that differ from other adult stem cells in differentiation potential, primitiveness, and biological function. As for which category belongs, there is still controversy in the current academic community, which needs to be further determined.

Table 1 Stem cell category

Stem Cell Category	Key Examples	Core Traits
Pluripotent Stem Cells	1. ESCs (in vitro, embryonic origin) 2. iPSCs (in vitro, reprogrammed from somatic cells) 3. VSELs (in vivo, postnatal origin)	λ Differentiate into all three germ layers; λ Retain embryonic-like stemness; λ ESCs/iPSCs require in vitro culture; VSELs exist naturally in postnatal tissues.
Adult Stem Cells	1. MSCs (bone marrow/adipose) 2. HSCs (bone marrow) 3. Neural stem cells (hippocampus)	λ Postnatal, tissue-resident; λ Tissue-specific multipotency (no cross-germ layer differentiation); λ Function in tissue homeostasis/repair.
Totipotent Stem Cells	Zygote, early cleavage-stage cells	λ Differentiate into all embryonic and extraembryonic tissues; λ Only exist in early embryos.

Stem cell biology

Stem cells are often referred to as "seed cells" for tissue regeneration. Compared with mature body cells, stem cells have some unique biological characteristics: (1) They belong to the non-differentiated cells, which maintain unlimited or low differentiation characteristics for life, and lack differentiation marks. The currently known stem cell markers include ESC-specific markers, HSC-specific markers, and MSC-specific markers; these markers (e.g., surface proteins, intracellular transcription factors) are used to identify and isolate distinct stem cell populations, as defined by their unique biological properties. (2) The position of the body is relatively constant. The body strictly controls the number of stem cells, and the number of tissues is minimal and decreases with age. The number and position of adult stem cells are relatively constant to adapt to the maintenance and repair of specific tissues and organs, and to maintain their stability; (3) have the ability to renew themselves. It can divide and proliferate indefinitely and remain in a static state for a long time. Internal manifestations are all cells that can form tissues and maintain their quantity, and in vitro, it is manifested as cloning growth; (4) Potential differentiation. It can be differentiated into various types of tissue cells, and it also has the plasticity of differentiation and development, but the differential potential of different stem cells has different potentials. In a specific environment, it can be induced to differentiate into a type of cell not related to development; (5) Slow division cycle. Most stem cells are in a relatively static state, dividing infrequently and living for a long time. It is only when tissues need regular renewal or replacement that stem cell proliferative activity is activated; (6) Have the ability to migrate and return to the nest. The interaction between the special receptor on the stem cell surface and the ligand in the extracellular matrix can trigger the signaling pathway and move the cell to a specific location. MSCs are sometimes referred to as 'mesenchymal stromal cells' in literature, reflecting their dual role: they exhibit stem cell properties (self-renewal, mesodermal multipotency) and stromal support functions (e.g., immune regulation, tissue microenvironment maintenance). This manuscript uses 'MSCs' to align with clinical and regulatory conventions, while acknowledging their stromal contributions. The ability to return to the nest is the ability of stem cells to migrate to specific tissues or organs. This ability is essential for stem cells to repair and regenerate [6–12]. Notably, in clinical applications, MSCs' therapeutic efficacy is primarily driven by their paracrine secretome (e.g., EVs, cytokines) that regulates immunity and tissue microenvironments, while their direct differentiation into tissue-specific cells plays a supplementary role in localized repair (e.g., cartilage or bone defects).

Development of stem cell technology

The introduction of the term "stem cell" by Ernst Haeckel in 1868 laid the groundwork for exploring these unique cells that could give rise to all cell types in an organism [13, 14]. The foundation was further solidified in 1888 through the pioneering work of Theodor Heinrich Boveri and Valentin Haecker, who narrowed down the properties that define a stem cell in the context of embryonic development [15, 16]. The development of stem cell therapy began with early exploratory attempts, such as the first reported attempt at bone marrow transplantation for aplastic anemia in 1939, though this trial was not successful. The field advanced substantially with the first allogeneic hematopoietic stem cell transplantation for aplastic anemia conducted by Dr. Donnall Thomas in 1957 [17, 18]. Thomas's work was groundbreaking, albeit fraught with risks, and provided a critical foundation for future advancements in stem cell transplantation [19, 20]. George Mathe's 1958 achievement in using bone marrow transplantation to treat researchers exposed to radiation further demonstrated the potential of stem cell therapy in treating conditions arising from external stressors on the body [21, 22]. These historical milestones have paved the way for the ongoing exploration and application of stem cell technology in various medical fields, including regenerative medicine and bone marrow transplantation.

In 1969, Canadian scientists McCulloch and Till first demonstrated, for the first time, the existence of stem cells in the blood and discovered that hematopoietic stem cells were capable of differentiating into hundreds of different types of human cells [23]. Stem cell medical technology applications began to quickly develop following the first bone marrow transplant surgery in 1968, after the use of hematopoietic stem cells [24]. Governments from various countries introduced policies to support the development of the stem cell industry starting in 2000, leading to the normalization of regulations and further advancements in the field [25]. Among these, the history of iPSCs was relatively short [26]. In 2011, a team led by Professor Yamanaka of Kyoto University, Japan, built on their 2006 foundational work—where they initially tested 24 candidate pluripotency-related genes—and further optimized reprogramming protocols: using viral vectors to deliver a refined set of transcription factors into adult mouse skin cells, they efficiently reprogrammed these cells into iPSCs that closely resembled embryonic stem cells (ESCs) [27]. This pioneering achievement opened the field of iPSC research. Over subsequent experiments, Yamanaka's team narrowed down the essential transcription factors to a maximum of four (Oct4, Sox2, Klf4, c-Myc). It was for his pioneering contributions to iPSC research—alongside Professor John B. Gurdon, who laid the foundational groundwork for nuclear reprogramming through his 1962 experiments on frog egg nuclear transplantation—that Professor Yamanaka shared the Nobel Prize in Physiology or Medicine in 2012 [28–30]. In 2013, the team led by Masayo Takahashi in Japan successfully repurposed the skin cells of two patients suffering from age-related macular degeneration into iPSCs [31]. They then induced these cells to form retinal pigment epithelial (RPE) cells, which they implanted into a 70-year-old patient's right eye in the first-ever clinical trial in 2014, thereby restoring her vision. Confirmation of this successful treatment was established several years later [32–35]. Stem cell milestones are shown in Fig. 1.

A decade ago, VSELs were indeed mired in three core disputes: (1) doubts about their authentic existence (attributed to extreme rarity, ~0.01–0.02% of bone marrow mononuclear cells, and crude isolation methods that led to contamination by MSCs or cell debris); (2) skepticism about their purported pluripotency (with inconsistent detection of pluripotent markers like Oct4/Nanog dismissed as experimental artifacts); and (3) questions about their physiological relevance (viewed as a "theoretical cell type" with no proven role in tissue regeneration). However, driven by technological innovations, rigorous functional validation, and clinical translational exploration, the past 10 years have witnessed transformative advances that have systematically resolved these controversies, establishing VSELs as a well-characterized, clinically promising stem cell subset.

Technological breakthroughs have first addressed the "existence controversy" by standardizing VSEL isolation and characterization. Early studies relied on density gradient centrifugation, which failed to separate VSELs from smaller somatic cells or debris; today, a consensus protocol combining erythrocyte lysis, immunomagnetic sorting, and fluorescence-activated cell sorting (FACS) using the phenotypic signature $Lin^-/CD45^-/SSEA\text{-}4^+/Oct4^+$ achieves > 95% purity of VSELs from tissues like bone marrow, umbilical cord blood, and even follicular fluid [cited VSEL isolation protocols]. Complementing this, single-cell RNA sequencing (scRNA-seq) has eliminated ambiguity about VSEL identity: transcriptomic profiling confirms VSELs possess a unique gene expression signature—enriched for embryonic development pathways (e.g., POU5F1, NANOG) and tissue regeneration genes (e.g., CXCR4, KIT)—that is distinct from MSCs, hematopoietic stem cells (HSCs), and other somatic cells. For instance, a 2022 study using scRNA-seq on human bone marrow VSELs identified 123 genes specifically upregulated in VSELs, including pluripotency regulators not expressed in MSCs [cited scRNA-seq study]. Additionally, optimized in vitro culture systems—supplemented with a cocktail of growth factors (e.g., LIF, bFGF) and epigenetic modifiers (e.g., valproic acid)—now enable stable expansion of VSELs through 10 + passages while

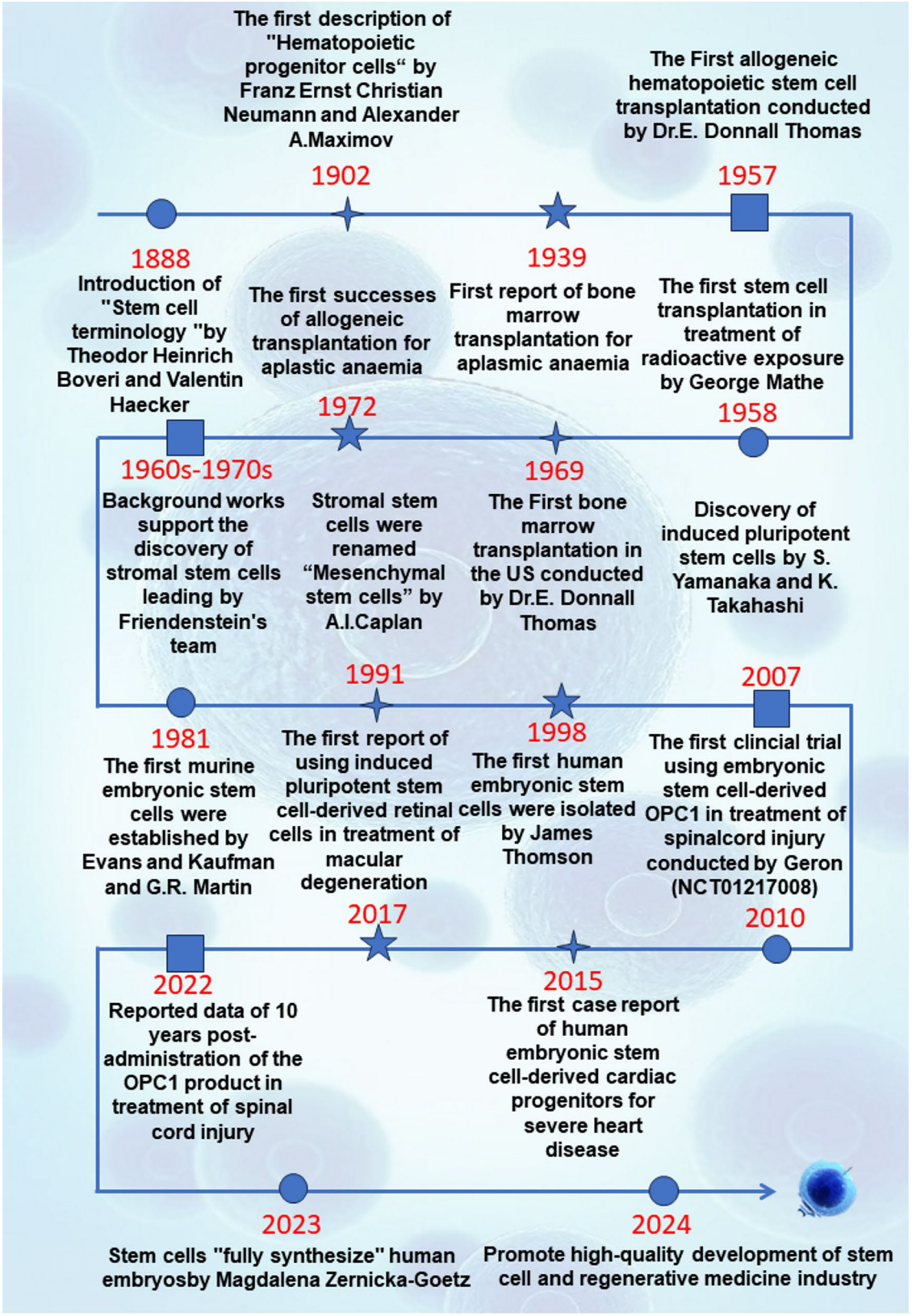

Fig. 1 The development of stem cells

preserving their pluripotency, addressing the historical challenge of VSELs being non-proliferative in culture.

Rigorous basic research has further resolved the "pluripotency and functional controversies" by providing definitive evidence of VSELs' cross-germ layer differentiation capacity and in vivo regenerative role. In vitro, under lineage-specific induction conditions, VSELs consistently differentiate into cells of all three germ layers: ectoderm (neurons expressing β-III tubulin and synaptophysin), mesoderm (contractile cardiomyocytes positive for troponin I and α-actinin), and endoderm (hepatocyte-like cells secreting albumin and urea) [cited VSEL differentiation studies]. Importantly, unlike induced pluripotent stem cells (iPSCs), VSELs exhibit "safe pluripotency": they do not form teratomas in nude mouse models, likely due to tight epigenetic constraints (e.g., hypermethylation of oncogenes like c-Myc) that prevent unregulated proliferation. In vivo, multiple animal models have confirmed VSELs' physiological function in tissue repair: in rodent models of acute myocardial infarction, VSELs mobilized to the infarct site via SDF-1/CXCR4 signaling differentiate into cardiomyocytes and endothelial cells, reducing left ventricular fibrosis by 35% and improving ejection fraction by 18% at 8 weeks post-transplant [cited cardiac repair study]; in chemotherapy-induced premature ovarian insufficiency (POI) models, ovarian-resident VSELs activated by MSC-secreted factors regenerate new oocytes, restoring menstrual cycles in 60% of treated mice—challenging the traditional dogma of a "fixed ovarian follicle pool" [cited ovarian regeneration study]. These findings directly refute earlier claims that VSELs lack functional relevance, positioning them as key mediators of endogenous tissue renewal.

Clinical translational progress over the past decade has further solidified VSELs' status as a viable therapeutic tool, moving beyond "theoretical potential" to preclinical and early clinical validation. In orthopedics, autologous VSELs combined with bioactive scaffolds (e.g., collagen-hydroxyapatite) have shown promise in treating critical-sized bone defects: a 2023 preclinical study in sheep demonstrated that VSEL-seeded scaffolds generated mineralized bone tissue with 90% of the mechanical strength of native bone within 3 months, outperforming MSC-seeded scaffolds [cited orthopedic study]. In cardiology, a phase I clinical trial (NCT05265358) evaluating autologous bone marrow VSEL transplantation for ischemic heart disease reported no adverse events (e.g., arrhythmia, tumorigenesis) in 15 patients followed for 12 months, with 8 patients showing a ≥ 20% reduction in myocardial scar size [cited clinical trial data]. In reproductive medicine, small-scale clinical studies in Germany and Egypt have explored activating endogenous ovarian VSELs via intraovarian injection of MSC-conditioned medium: 30% of patients with idiopathic POI regained regular menstrual cycles, and 2 patients achieved successful pregnancy—providing preliminary evidence of VSELs' clinical utility [cited reproductive study]. These advances, coupled with the establishment of VSEL-specific safety profiles (e.g., no long-term tumorigenesis in 12-month rodent follow-up), have addressed the final barrier of "clinical relevance" that once plagued VSEL research.

In summary, the past decade has seen VSELs evolve from a controversial concept to a well-validated stem cell subset. Technological innovations have confirmed their existence and purity, functional studies have validated their pluripotency and regenerative capacity, and clinical exploration has demonstrated their safety and preliminary efficacy—fully leaving behind the historical controversies. As VSEL research advances toward larger-scale clinical trials for degenerative diseases (e.g., osteoarthritis, Parkinson's disease) and tissue repair, they are increasingly recognized as a unique "in vivo pluripotent reserve" that bridges the gap between embryonic stem cells (ethical concerns) and MSCs (limited potency), holding great promise for regenerative medicine. We will explicitly integrate this progress into Sect. 1.3 (Stem Cell Technology Development) and Sect. 4 (Challenges and Opportunities) of the revised manuscript, ensuring readers fully grasp VSELs' transformative journey over the past decade.

The detection of OCT-4, NANOG, and SSEA4 in fetal tissues, follicular fluid, menstrual blood, and dental pulp does not imply that all cells in these tissues are pluripotent. Instead, this phenomenon can be attributed to four key mechanisms, which align with the biological complexity of stem cell populations in postnatal and fetal tissues:

Presence of endogenous primitive stem cells (e.g., VSELs)

VSELs are primitive, pluripotent stem cells that naturally exist in multiple postnatal and fetal tissues but are extremely rare and easily overlooked in conventional studies. VSELs retain embryonic stem cell (ESC)-like characteristics, including the expression of core pluripotent transcripts (OCT-4, NANOG) and surface markers (SSEA4) [cited literature on VSELs]. In tissues like menstrual blood (derived from endometrial tissue, which undergoes cyclic regeneration) and dental pulp (a niche for tissue repair), VSELs may serve as a "reserve pool" of pluripotent stem cells. Their low abundance means they are often not isolated or characterized separately in studies targeting MSCs, leading to the misattribution of pluripotent transcript signals to other cell types (e.g., MSCs).

Heterogeneity of mscs: subpopulations may express pluripotent markers (without pluripotent potential)

Mesenchymal stem cells (MSCs) in these tissues are not a homogeneous population—they consist of multiple subpopulations with varying degrees of maturity and differentiation potential. A small subset of immature MSC subpopulations may transiently express low levels of OCT-4 or NANOG during in vitro culture or in vivo activation (e.g., during tissue repair). However, this expression is not associated with pluripotent function: these subpopulations still only differentiate into mesodermal lineages (bone, cartilage, adipose cells), as confirmed by the manuscript's Sect. 1.4 (approved MSC products for bone/cartilage repair) and Sect. 2.4 (MSC therapy for knee osteoarthritis). The expression of pluripotent transcripts in these MSC subpopulations may reflect a "primitive state" rather than true pluripotency.

Non-pluripotent functions of "pluripotent transcripts"

OCT-4, NANOG, and SSEA4 are not exclusive markers of pluripotency—they also regulate non-pluripotent biological processes in adult tissues. For example: OCT-4 is involved in the self-renewal of adult stem cells (e.g., HSCs) and tissue regeneration, independent of pluripotency [relevant research citations]. NANOG modulates the proliferation and differentiation of MSCs, helping maintain their "stemness" (e.g., preventing premature differentiation into bone cells) rather than enabling cross-germ layer differentiation. Thus, the detection of these transcripts may reflect their role in maintaining adult stem cell homeostasis, not pluripotency.

Sensitivity of detection methods

Modern detection techniques (e.g., RT-qPCR, flow cytometry, immunofluorescence) are highly sensitive, capable of detecting low-abundance transcripts or proteins. In tissues like follicular fluid (which contains shed ovarian cells) or fetal tissues (which retain residual embryonic progenitors), even a small number of cells expressing pluripotent markers can generate detectable signals—this does not indicate widespread pluripotency in the tissue.

Global stem cell development progress

At present, there are 14 mesenchymal stem cell (MSC) products approved for marketing worldwide, including one autologous mesenchymal precursor cell from Australia (Table 2). The approved products mainly utilize the tissue repair and immune regulation functions of MSCs, and their indications include acute myocardial infarction, degenerative arthritis, amyotrophic lateral sclerosis, bone repair, graft-versus-host disease, Crohn's disease and perianal fistula, COVID-19, severe limb ischemia, and so on [36–44].

It is also worth mentioning that Mesoblast's bone marrow-derived mesenchymal stem cell therapy, Remestemcel-L submitted a BLA (Biologics License Application) again in 2022, but the FDA refused to approve it and required more data to further support the listing of Remestemcel-L [39, 40, 45]. This stem cell therapy has been launched in Japan and is the world's first mesenchymal stem cell product for the treatment of acute graft-versus-host disease. However, it has experienced twists and turns on the road to FDA approval. Although the FDA rejected this product in 2023, it is still possible to be listed.

At the same time, NurOwn, a mesenchymal stem cell drug developed by Brainstorm, also knocked on the door of the FDA again last year [46]. The product is used to fight amyotrophic lateral sclerosis. The BLA was submitted on September 9, 2022, and the FDA's refuse-to-file (RTF) letter was received on November 8, 2022. After communication, consultation, and rectification, the FDA resumed its BLA review on February 7, 2023, and set the PDUFA (Prescription Drug User Fee Amendments) target date as December 8, 2023. On September 27, 2023, the FDA Cell, Tissue, and Gene Therapy Advisory Committee opposed NurOwn's marketing application with an overwhelming result of 1:17, determining that there was insufficient effective evidence for its treatment of mild to moderate ALS. Finally, on December 7, the FDA held a special program assessment (SPA) on NurOwn for the treatment of ALS. The results of the meeting provided a clear path for the planned Phase 3b trial, indicating that NurOwn is still an unknown distance away from the time of listing. The BLA experience of the two MSC drugs at the FDA also reflects that the regulatory and CMC (Chemistry, Manufacturing, and Control) challenges of stem cell drugs still require the joint efforts of the industry to improve and break through [47–51].

Notwithstanding this, the stem cell therapy market in China has experienced significant growth over the past two years. As of July 2023, the country has secured nearly 60 Investigational New Drug (IND) approvals for 35 mesenchymal stem cell (MSC) therapies, addressing more than 20 medical indications. Furthermore, data indicate that in 2023, the Center for Drug Evaluation (CDE) in China accepted a total of 39 clinical trial applications for stem cell drugs, involving 27 different companies. The majority of these applications pertain to mesenchymal stem cell products, particularly umbilical cord-derived mesenchymal stem cells. The medical indications primarily encompass liver diseases, such as cirrhosis and liver failure, degenerative conditions, including knee osteoarthritis, and autoimmune disorders, such as lupus nephritis [52–54]. Clinical transformation has ushered in a "golden period" of development, and the prospects are promising.

Table 2 Stem cell products currently on the market

Approved Locations	Approved year	Drug name	The source of the cell	Indications
American	2009	Prochymal	Allogeneic bone marrow MSCs	GVHD (graft-versus-host disease)
American	2010		Allogeneic bone marrow MSCs	Type I diabetes
Canada	2012	Remestemcel-L	Allogeneic bone marrow MSCs	SR-aGVHD
New Zealand	2012			
Japan	2015			
New Zealand	2012	Prochymal	Allogeneic bone marrow MSCs	GVHD
Korea Republic	2011	Hearticellgram®-AMI	Autologous bone marrow MSCs	Acute myocardial infarction(AMI)
	2012	Cartistem	Allogeneic cord blood MSCs	Cartilage injury and degenerative joint disease
	2012	Cuepistem	Autologous fat MSCs	Complex Crohn's disease complicated by anal fistula
	2014	NeuroNATA-R	Autologous bone marrow MSCs	Amyotrophic lateral sclerosis (ALS)
	2020	Cellgram-AKI	Allogeneic bone marrow MSCs	COVID-19
Japan	2016	Temcell	Allogeneic bone marrow MSCs	GVHD
	2018	Stemirac	Autologous bone marrow MSCs	Spinal cord injury
	2018	RNL-Astrostem	Autologous fat MSCs	Alzheimer disease
European Union	2018	Alofisel	Allogeneic fat MSCs	Crohn's disease and perianal fistula
Japan	2021			
India	2010	CardioRel	Autologous bone marrow MSCs	MI (Myocardial infarction)
	2016	Stempeucel	Allogeneic bone marrow MSCs	Severe limb ischemia due to Buerger's disease
	2020			Severe limb ischemia due to atherosclerosis
Australia	2010	MPC(Mesenchymal Precursor Cell)	Autologous stromal progenitor cells	Bone repair

Note: All listed tissues (bone marrow, adipose, cord blood, follicular fluid) harbor VSELs, a pluripotent stem cell subset. Wharton jelly (umbilical cord) is an unlisted but rich source of VSELs (0.1–0.2% frequency) with strong regenerative potential. All approved MSC products listed rely on paracrine-mediated immune regulation or tissue microenvironment improvement for efficacy; direct differentiation into target cells is not the primary mechanism

Global regulatory comparison

We will systematically compare regulatory frameworks for stem cell therapies across major regions, highlighting similarities, differences, and their impacts on clinical translation.

U.S. FDA: Classifies most stem cell therapies as "Biologics License Applications (BLAs)" under 351(a) of the Public Health Service Act, with strict requirements for Chemistry, Manufacturing, and Controls (CMC) and long-term safety data (e.g., the 2023 refusal of NurOwn's BLA due to insufficient efficacy evidence [46]).

EU EMA: Regulates stem cells as "Advanced Therapy Medicinal Products (ATMPs)" (subdivided into Tissue-Engineered Products, Gene Therapies, and Cell Therapies), with a centralized approval process and emphasis on "risk-based classification" (e.g., lower-risk autologous MSCs vs. higher-risk iPSC-derived products [44]).

Japan PMDA: Implements the "Regenerative Medicine Safety Act," which allows "conditional and time-limited approval" for unmet medical needs (e.g., the 2014 approval of iPSC-derived RPE cells for macular degeneration [32]), accelerating access while requiring post-marketing surveillance.

China NMPA: Contextualize its "dual-track system" (IND pathway for drugs vs. clinical research pathway for technical applications) within the global landscape, noting how it balances innovation (e.g., 60 IND approvals by 2023 [52]) and risk control (e.g., strict donor eligibility for allogeneic MSCs [53]).

Remestemcel-L (Mesoblast's bone marrow MSC therapy) as an example, which was approved in Canada (2012), Japan (2016), and the EU (for pediatric GVHD), but repeatedly rejected by the FDA (2022–2023) due to disagreements on clinical endpoint validation [35, 38]. This case will illustrate how regulatory differences in "efficacy evidence standards" delay global clinical access, a key barrier to bridging research and application.

Clinical application of stem cells

Stem cell therapy involves the transplantation of healthy stem cells into a patient or the individual's own body to facilitate the repair of diseased cells or the regeneration of functional cells and tissues. This therapeutic approach is considered a cornerstone in the treatment of various diseases. Presently, the primary clinical applications of stem cell therapy encompass a range of medical conditions, as

illustrated in Fig. 2. The spectrum of diseases investigated in stem cell clinical research predominantly includes ulcerative colitis, ovarian insufficiency, osteoarthritis, lupus nephritis, psoriasis, spinal cord injury, and acute myocardial infarction, among others.

Blood system diseases

Blood system diseases encompass a range of disorders affecting the hematopoietic and lymphatic systems, including conditions such as anemia, leukemia, and lymphoma. The utilization of stem cells in the management of these diseases is primarily exemplified through hematopoietic stem cell transplantation, which has proven to be an effective therapeutic approach for various blood disorders. Hematopoietic stem cells possess remarkable long-term self-renewal capabilities and the potential for multilineage differentiation. They are capable of differentiating into red blood cells, white blood cells, platelets, and other hematological components, thereby playing a crucial role in sustaining normal hematological function and supporting the immune system in the human body [55].

Hematopoietic stem cell transplantation serves as a therapeutic intervention for a range of hematological disorders, encompassing both malignant conditions, such as acute leukemia, chronic myeloid leukemia, lymphoma, multiple myeloma, and myelodysplastic syndromes, as well as certain non-malignant disorders, including severe aplastic anemia and thalassemia. Notably, gene editing of hematopoietic stem cells represents a significant focus of contemporary research and development in this field.

For non-malignant tumor diseases, Casgevy, developed by Vertex and CRISPR, is a therapy that uses CRISPR/Cas9 gene editing technology to modify the patient's hematopoietic stem cells and has been approved for the treatment of sickle cell disease (SCD) [56]. The high cost of ex vivo gene editing ($2.2 million per patient for Casgevy) and limited access in low- and middle-income countries—key barriers to scaling clinical application. Lyfgenia, which targets the same indication, modifies the patient's hematopoietic stem cell genes through lentiviral vectors and then infuses these modified stem cells back into the patient's body [57].

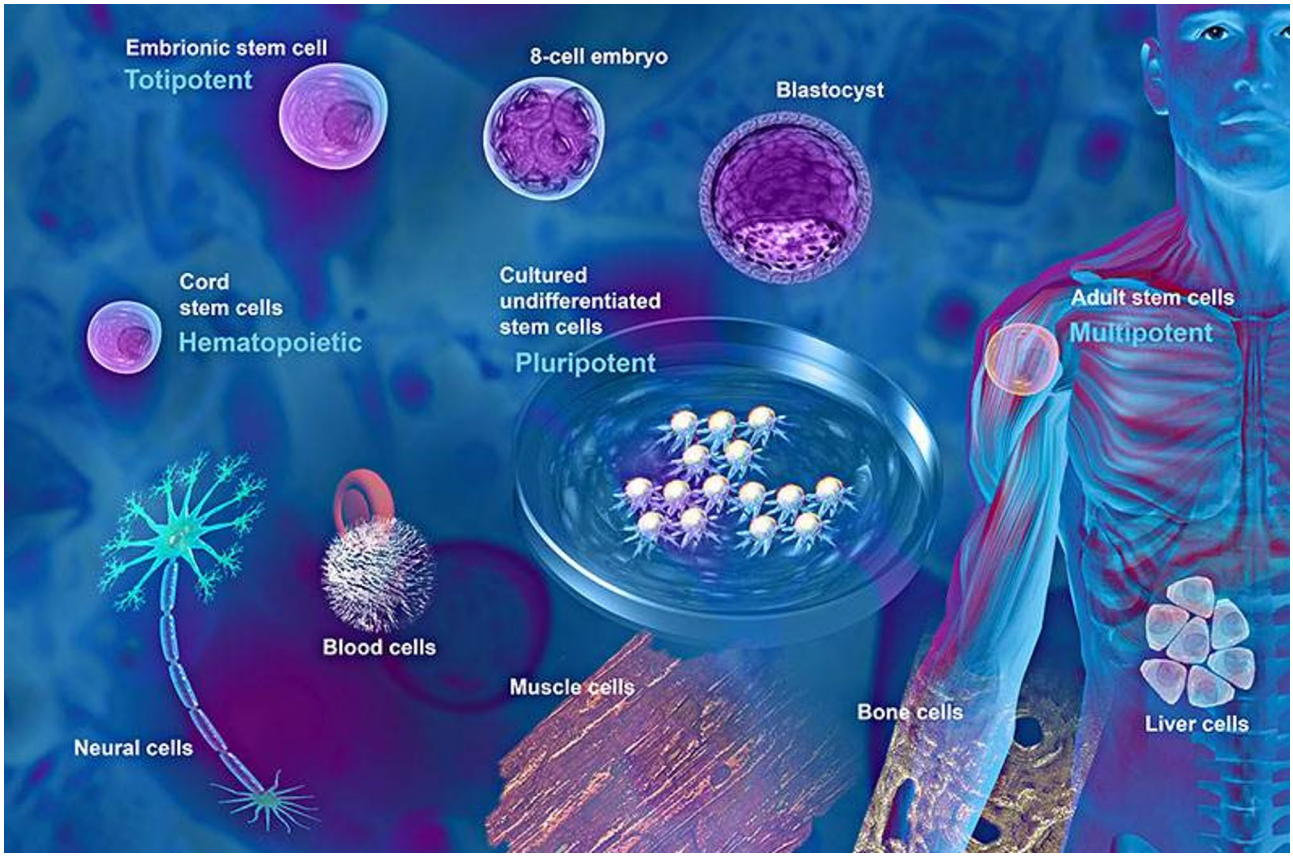

Fig. 2 Stem cell therapy is an emerging treatment method. It utilizes the self-renewal ability and multidirectional differentiation potential of stem cells to treat a variety of diseases by transplanting healthy stem cells into the patient's body to replace damaged or diseased cells. This treatment method has a wide range of applicability and can be used to treat nervous system diseases, blood system diseases, immune system diseases, and endocrine system diseases

In terms of thalassemia, domestic companies such as Bangyao Bio, Boya Gene, Ruifeng Bio, Bendao Gene, Kanglin Bio, and Hemu Gene have all entered the market, and the technical means used are mainly CRISPR/Cas9 and lentiviral vectors.

Nervous system diseases

Nervous system diseases encompass a range of disorders affecting both the central and peripheral nervous systems. These conditions include, but are not limited to, neuroimmune disorders, infections of the central nervous system, peripheral neuropathies, movement disorders, and epilepsy. Stem cells possess the potential to replace deceased or impaired nerve cells through mechanisms of cell replacement, facilitate the repair of damaged neural networks, and secrete a variety of neurotrophic and nutritional factors that can stimulate nerve cell activation and promote the regeneration and reconstruction of new cells. Recent reports indicate that stem cells are being utilized in the treatment of various neurological disorders [58, 59].

Parkinson's disease (PD) is a degenerative disease of the central nervous system. Its cause is still unclear. According to research, it is speculated that this is because the substantia nigra cells in the brain degenerate and cannot produce enough dopamine. Stem cell treatment of PD has certain advantages [60]. It is a feasible cell replacement treatment for Parkinson's disease and one of the hot directions of stem cell research [61]. The types of stem cells involved in the research include induced PSCs, mesenchymal stem cells (MSCs), neural stem cells, embryonic stem cells, and so on [62].

In May 2023, Bayer announced the results of a Phase 1 clinical study of its stem cell-derived therapy BRT-DA01 for the treatment of Parkinson's disease (NCT05897957) [63]. The therapy was safe and tolerable in 12 subjects in both the low-dose and high-dose groups. No serious adverse events related to the therapy occurred within one year, and some of them had their symptoms relieved. BRT-DA01 (iPSC-derived dopamine neurons) Phase 1 extension data (NCT05897957): 18-month follow-up showing 7/12 patients maintained ≥ 30% reduction in UPDRS III scores (motor symptoms), with no dyskinesia (a common side effect of levodopa). The challenge of "neuronal integration"—only 15–20% of transplanted iPSC-derived neurons form functional synapses with host tissue, limiting long-term efficacy [62].

For neuromyelitis optica spectrum disease (NMO), Fu et al. reported on 15 patients with NMO spectrum disease who received bone marrow MSCs treatment. The patients were intravenously injected with approximately 108 autologous bone marrow MSCs and followed up for 2 years. Among them, 13 patients did not experience clinical relapse, and their EDSS scores improved significantly. Another study included 12 patients who used autologous MSCs to treat NMO. After careful care and clinical treatment, the condition of all 12 patients improved, and they were discharged from the hospital; 2 of them recovered completely [64, 65].

In the field of multiple sclerosis (MS), Riordan et al. observed and reported the clinical efficacy of stem cells on 20 MS patients, of which 15 patients had a baseline diagnosis of relapsing-remitting MS, 4 had primary progressive MS, and 1 had secondary progressive MS. Follow-up showed that all patients had clinical symptoms relieved, EDSS scores significantly improved, and there was no deterioration or relapse. In addition, stem cells have made some progress in treating autoimmune encephalitis, myasthenia gravis, Alzheimer's disease, spinal cord injury, and other diseases [66, 67].

In addition, companies such as Zhongsheng Source, Yuesai Bio, and Ruizhen Regenerative Medicine have also made inroads in the field of iPSC cell drugs for the treatment of CNS diseases, and are accelerating their progress.

Endocrine system diseases

Endocrine and metabolic diseases are often caused by endocrine gland lesions, involving dysfunction of multiple other system organs [68]. Stem cells possess the capability to differentiate into a range of functional cell types within the human endocrine system, including thyroid follicular epithelial cells, adrenal epithelial cells, and adrenal cells, among others [69]. The newly generated functional cells possess the capability to substitute necrotic cells, thereby reinstating the interdependent regulation among the endocrine, nervous, and immune systems, which collectively contribute to the maintenance of homeostasis within the organism.

The most common endocrine system disease is diabetes, which is also the direction in which stem cells are more widely used in endocrine system diseases. Stem cell-based therapies may be able to fundamentally cure diabetes, such as transplantation of islet cells or islet organoids derived from stem cells, mesenchymal stem cells/induced PSCs for the treatment of diabetes, etc., which provides new treatment ideas for the disease [70, 71].

In July 2023, based on the filing of stem cell clinical research by the National Health Commission, Tianjin First Central Hospital and Peking University Stem Cell Center worked together to complete the world's first pancreatic islet-like cell transplantation surgery differentiated from canine reprogrammed induced pluripotent stem cells (CiPSC) in type 1 diabetes subjects. This treatment technology is expected to become an ideal solution for completely curing T1DM (Type 1 diabetes mellitus) [72, 73].

The company currently conducting iPSC clinical trials for diabetes treatment worldwide is mainly Vertex. In March 2023, Vertex announced that the US FDA had approved its IND for VX-264 [74]. VX-264 is a stem cell-derived, fully differentiated pancreatic islet cell therapy encapsulated in an immune protection device for the treatment of T1DM without immunosuppressants. In December 2024, Vertex's VX-880 (iPSC-derived islet cells): 24-month data from Phase 1/2 trials (NCT04786262) showing 2/3 patients achieved insulin independence, with HbA1c levels maintained below 7% without immunosuppressants (due to the device's immune protection [75]. The limited durability of iPSC islets—1 patient lost insulin independence at 18 months due to gradual device fibrosis, highlighting the need for better biocompatible materials.

Diseases of the musculoskeletal system

Diseases of the musculoskeletal system mainly include injuries or diseases of muscles, ligaments, joints, and bones, which may be caused by trauma, inflammation, or other factors. The potential application of stem cells in sports medicine, including the treatment of ligament injuries, tendinitis, cartilage defects, muscle injuries, fractures, and nerve injuries, can accelerate healing, reduce inflammation and pain, improve tissue regeneration, and enhance motor function [76, 77].

For osteoarthritis, Vega et al. divided 30 patients with chronic knee pain, ineffective conservative treatment, and radiological evidence of osteoarthritis into two groups. The experimental group was given intra-articular injection of allogeneic bone marrow mesenchymal stem cells, and the control group was given hyaluronic acid. They were followed up for 1 year to evaluate their pain, disability, and quality of life. The results showed that the pain index of the treatment group was significantly improved, and the quality of cartilage was significantly improved [78].

In April 2023, Sibman Bio officially announced the launch of the company's Phase 3 clinical trial of AlloJoin®, an allogeneic human adipose mesenchymal progenitor cell injection [79]. The preliminary Phase 2 data show AlloJoin® exerts good safety and efficacy in knee osteoarthritis by secreting anti-inflammatory cytokines (IL-4) and trophic factors (BMP-7) to activate endogenous chondrocyte repair, rather than extensive differentiation into chondrocytes. AlloJoin® is China's first independently developed innovative stem cell drug that has entered Phase 2 clinical trials with implicit approval from the CDE. It is also China's first stem cell drug for knee osteoarthritis to enter Phase 3 clinical trials [80].

Cardiovascular diseases

There are various types of cardiovascular diseases, including heart failure, acute myocardial infarction (MI), arrhythmia, etc. Stem cells have the potential to repair damaged myocardium and can differentiate into related cells, providing new ideas for the treatment of cardiovascular diseases [81, 82].

In September 2023, Heartseed announced a case report from a Phase 1/2 clinical trial of its stem cell-derived therapy HS-001 in the treatment of two patients with advanced heart failure. The report noted that both patients, who initially suffered from severe heart failure, experienced reverse remodeling and improved cardiac function at 26 weeks post-dose. Data show that at 26 weeks after treatment, the patient's LVEDV (left ventricular end-diastolic volume) was reduced, LVEF (left ventricular ejection fraction) was significantly improved, and NT-proBNP (N-terminal B-type natriuretic peptide precursor) was significantly increased [83].

In August 2023, the domestic AIRP Regenerative Medicine "Clinical Research on Transepicardial Injection of Human iPSC-Derived Cardiomyocyte Injection (HiCM-188) for the Treatment of Severe Chronic Ischemic Heart Failure" project launch meeting was held at TEDA International Cardiovascular Disease Held at the hospital, this is a Phase 1/2a clinical trial that will explore the safety and effectiveness of intramyocardial injection of HiCM-188 in the treatment of patients with severe chronic ischemic heart failure [84].

Previously, a research paper published in the Journal of the American College of Cardiology showed that using mesenchymal precursor cells (MPCs) to treat patients with chronic heart failure can improve the prognosis of heart failure patients in the long term and significantly reduce their heart attacks. or incidence of stroke, MPC therapy has synergistic and additive effects with current heart failure treatments [85, 86].

Anti-aging

During the aging process, the number and function of stem cells in the human body will gradually decline, leading to the gradual decline of the function of tissues and organs. The principle of stem cell anti-aging is to provide the body with highly active exogenous adult stem cells, allowing these adult stem cells to play the role of cell renewal, tissue repair, and immune regulation in the body so that the aging body tissues and organs can be repaired and regenerated. The functions of young tissues and organs can be restored, ultimately achieving anti-aging [87].

In addition, emerging studies suggest that stem cells may exert a potential beneficial effect on skin anti-aging, possibly by activating the function of epidermal cells and restoring the normal physiological function of cells,

thereby restoring the skin's firmness and elasticity and rejuvenating the face. At present, the application of stem cell drugs in the field of aging is still in the research and exploration stage, and further clinical trials and verification are needed [88–91]. Still, they have already been applied in the field of medical beauty.

Analysis of the stem cell industry market

After years of development, the domestic stem cell industry has formed a relatively complete stem cell industry chain. The industry chain is mainly composed of upstream collection and storage, midstream technology development and drug development, and downstream treatment and application. The industry mainly includes the stem cell treatment service business, the stem cell storage business, and the stem cell pharmaceutical business. Among them, the upstream is the most mature link and the most basic and front-end business in the stem cell medical industry; the midstream and downstream need to be further expanded. Most of them are still in the early preclinical stage or preclinical stage, and the market is still in a relatively early stage and needs further development. Stem cells have a wide range of applications. Although the industry chain still needs to be gradually developed, its market prospects are relatively impressive.

According to Precedence Research data, the global stem cell therapy market size is US$14.8 billion in 2023, estimated to be US$11.22 billion in 2022, and is expected to reach around US$31.41 billion in 2030 (Fig. 3A). It will grow at a compound annual growth rate of 13.73% during the forecast period from 2023 to 2030 (Fig. 3B). Public data shows that the scale of my country's stem cell medical market has grown from 6.2 billion yuan in 2012 to 78.5 billion yuan in 2019, with a compound growth rate of 32.59%, far higher than the global growth rate (Fig. 3C). According to market research, China's stem cell market sales revenue reached US$14.0 billion in 2023 and is expected to reach US$3,030 million in 2030, with a compound annual growth rate (CAGR) of 43.56% during 2022–2030 (Fig. 3D) [92].

Upstream - stem cell collection and storage business

Stem cell collection and storage is the upstream link of the stem cell industry chain [93]. Its main business model is the collection of stem cell materials such as umbilical cord blood stem cells, umbilical cord mesenchymal stem cells, adipose stem cells, teeth, menstrual blood, amniotic membrane, etc., mainly mesenchymal and hematopoietic stem cells, and storage through specific technologies and equipment to maintain their activity and function. According to public information disclosure, According to public information disclosure, more than 40,000 companies are engaged in the stem cell storage business nationwide in China, and the business model is divided

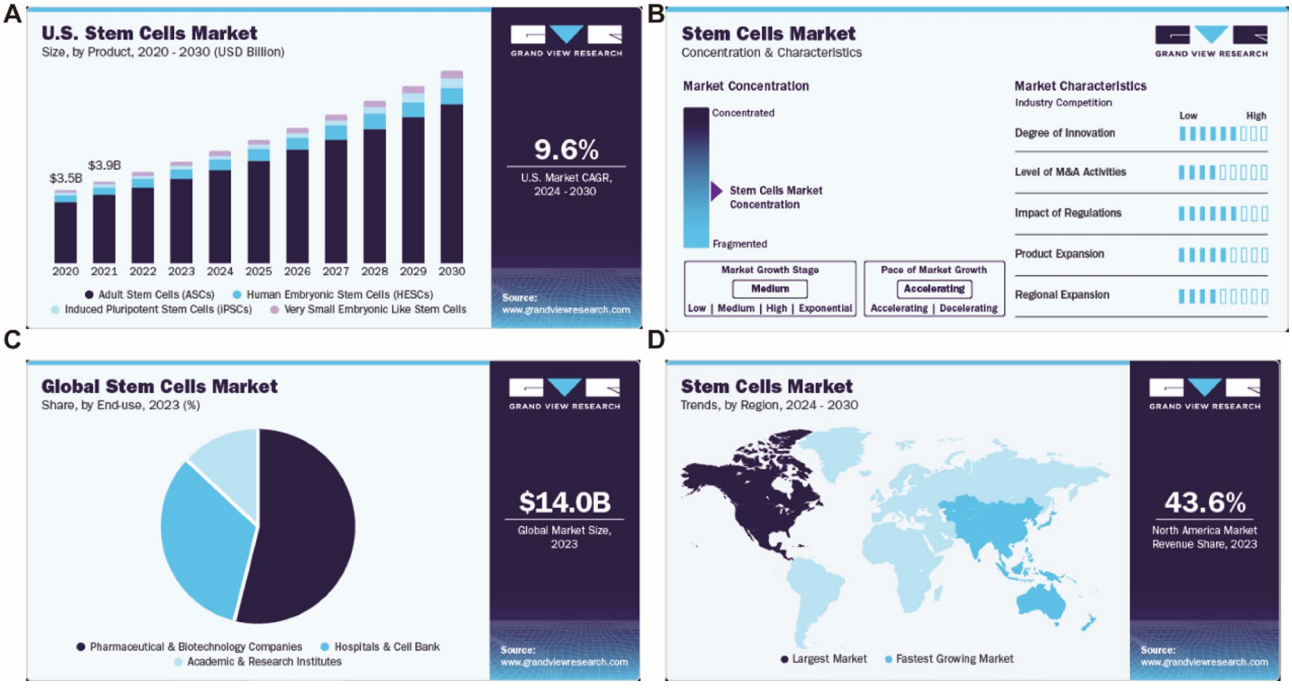

Fig. 3 Analysis of the stem cell industry market (A) The global stem cells market size was valued at USD 14.80 billion in 2023 and is expected to grow at a compound annual growth rate (CAGR) of 11.43% from 2024 to 2030. (B) The market growth stage is moderate, and the pace of the market growth is accelerating. (C) The pharmaceutical and biotechnology companies segment captured the largest market share of 53.76% in 2023. (D) North America accounted for the largest revenue share of 43.56% in 2023. The presence of innovators and key market players has resulted in higher penetration of market products in the region

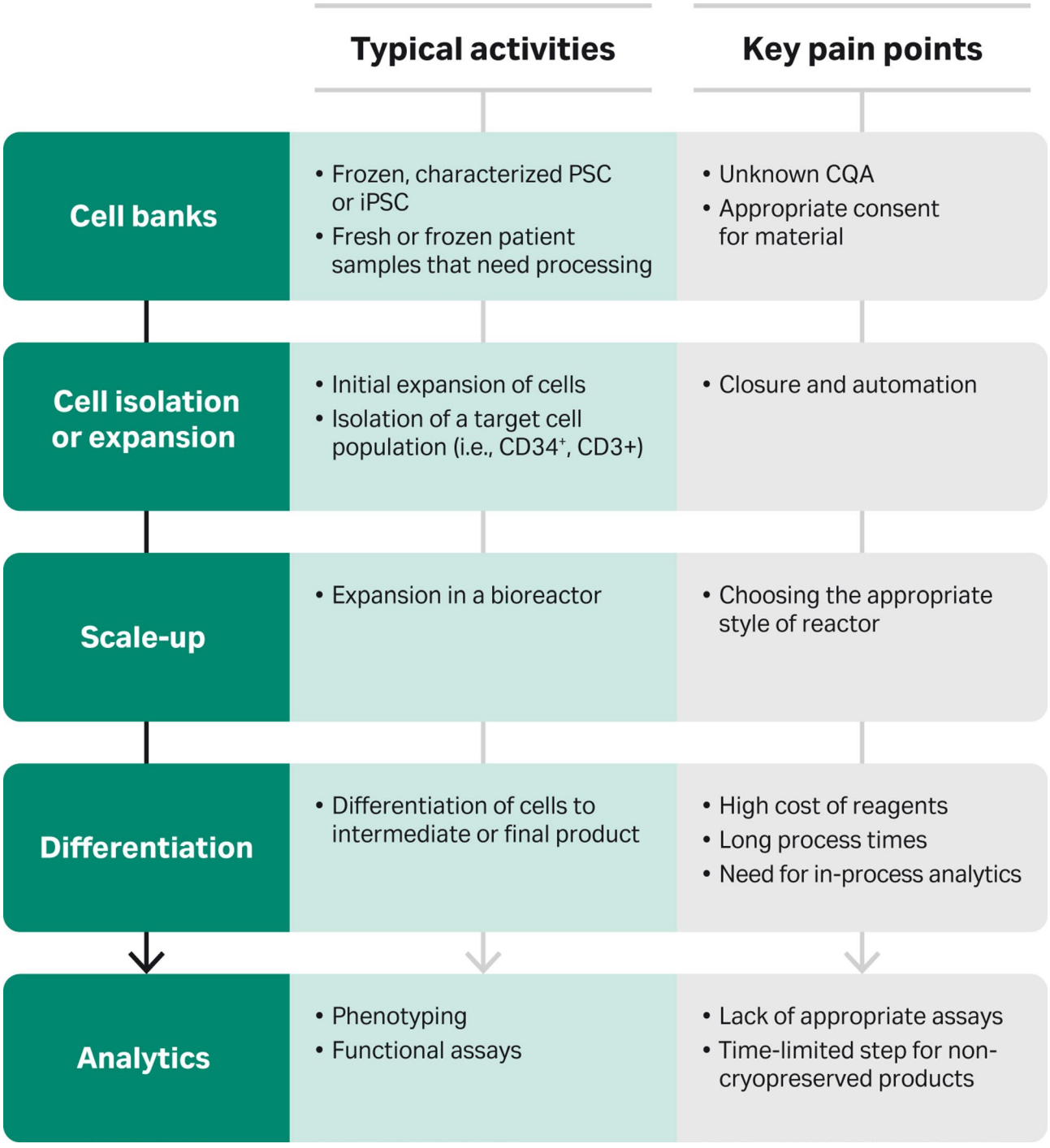

Fig. 4 Workflow, typical activities, and key pain points for upstream PSC processing

into public and autologous banks. Affected by external favorable environmental factors, the market size is expected to expand further in the future. At present, the umbilical cord blood hematopoietic stem cell bank and the umbilical cord mesenchymal stem cell bank are relatively mature, and the storage of dental pulp, fat, menstrual blood, and other types of stem cells is also in the ascendant. VSELs are ubiquitous in upstream collection tissues (e.g., bone marrow, adipose, follicular fluid) and are particularly enriched in Wharton jelly, representing a promising primitive stem cell source for regenerative medicine. The iPSC cell bank started late and is still in its infancy, but its development momentum is strong (Fig. 4) [94]. It is reported that listed stem cell companies have three major characteristics in the revenue of cell storage and preparation business, the proportion

of related business revenue is decreasing year by year, the gross profit margin of the business is maintained at around 80% all year round, and the regional leading effect is more obvious [95].

Midstream - stem cell drug research and development

Midstream enterprises mainly include various enterprises engaged in stem cell preparation, development of stem cell drugs, and other stem cell technology and product research and development, and are also the core of the entire industry chain. More than 60 domestic enterprises have deployed stem cells (including iPSC), and they are promoting the development of stem cell technology through continuous innovation.

In terms of stem cell proliferation, midstream enterprises use advanced cell culture technology to ensure that stem cells can maintain a good growth state and proliferation ability in an in vitro environment. This provides a large number of cell resources for subsequent clinical research and downstream applications and also lays a solid foundation for the research and development of stem cell drugs. In terms of stem cell drug research and development, midstream enterprises continue to explore their potential applications in disease treatment and strive to clinically transform scientific research results [96]. In the future, with the continuous development and maturity of stem cell technology, the role of midstream enterprises in the stem cell industry will become more prominent, injecting more power and vitality into the development of the entire industry.

In addition, with the popularity of iPSC and stem cell-derived exosomes, some new innovative technology companies based on iPSC and exosomes have begun to emerge, and a new wave of investment has followed, and they have begun to enter this emerging field. In addition to drug research and development, stem cell-based technologies for medical beauty (e.g., stem cell-derived exosomes for skin rejuvenation, MSC-conditioned medium for wound repair) will also be one of the future hot spots for stem cell development.

Downstream - consumer application field

The downstream links of the stem cell industry chain include hospitals and enterprises that have deployed downstream consumer fields [97]. Currently, the hospitals engaged in stem cell treatment are mainly military hospitals, such as Beijing 302 Hospital, Navy General Hospital, Armed Police General Hospital, etc. In the field of consumer applications, stem cells are mostly used in medical beauty and anti-aging health care. Therefore, the downstream enterprises are mainly based on stem cell health care, mainly distributed in major cities such as Beijing, Shanghai, Guangzhou, and Shenzhen, as well as Boao, Hainan, Qinhuangdao, Hebei, and other regions with policy advantages of trial implementation. With the relaxation of policies, the downstream will gradually develop in the future.

Challenges and opportunities of clinical transformation of stem cell therapy

Stem cells have high self-renewal and differentiation potential and can be widely used to treat a variety of diseases. The key to making stem cells truly benefit the majority of patients lies in clinical transformation. Clinical transformation can promote research to the clinic, and then it may be put on the market and become a treatment method that patients can choose. There are many types of stem cells, among which the types with more clinical transformation include hematopoietic stem cells, mesenchymal stem cells, and iPSCs; despite the different types, the clinical transformation challenges faced by these stem cells are common.

Tumorigenicity

Stem cell therapy has the potential for proliferation, but under certain conditions, stem cells may proliferate uncontrollably, forming uncontrolled cell clusters and causing tumor risks [98]. The retention of undifferentiated and/or immature cells in the final cell products differentiated from stem cells, or the occurrence of gene mutations in stem cells during in vitro culture, may lead to tumorigenicity. In addition, if the reprogramming factors of iPSC remain active in cells, they may also induce tumors.

Taking iPSC as an example, methods to reduce the risk of tumorigenicity include establishing effective in vitro-directed differentiation methods and forming more stringent purification procedures to meet the safety standards set by clinical trials. Secondly, the reprogramming factor c-Myc is one of the most well-characterized oncogenes in human cancer, and its abnormal overexpression or activation usually plays a driving role in tumorigenesis. Studies have shown that chimeric mice induced to form iPSCs by retroviral transfection of four reprogramming factors often form tumors.

Therefore, in the current reprogramming process, c-Myc can be replaced with the non-oncogene L-Myc and the regulatory gene Lin28, and attempts are being made to use technologies other than virus-mediated to complete the reprogramming process. In addition, the use of transcription factors such as Oct3/4, Klf4, LRH1, and GLS1 can shorten the reprogramming time of iPSC cells while improving the stemness of iPSC cells [99]. Moreover, with the application of gene editing technology, gene editing tools such as CRISPR/Cas9 can be used to remove or modify genes that may cause tumor formation, or enhance differentiation regulatory genes, further improving safety and reducing tumorigenic risks [100].

For example, Shize Bio has four major technology platforms that can support the rapid and efficient reprogramming of somatic cells into PSCs, as well as the induction of human PSCs to differentiate into neurons (glial cells and other functional cell types), and can efficiently and stably prepare specialized human glial cells and other functional cell types in different brain regions in vitro. Yuesai Bio has established an innovative reprogramming technology platform, a stem cell differentiation platform, a high-precision gene editing platform, and SISBAR (single-cell split barcoding) lineage tracing technology, which also provides strong support for the development of stem cell products.

Heterogeneity

Stem cells have pluripotency and the potential for proliferation, but different cell lines have different morphologies, growth curves, gene expression, and the tendency to differentiate into various cell lineages. In addition, possible stimuli during the culture process have brought obstacles to their application.

Studies have found that only mESCs from 129 strains of mice have a good ability to produce chimeric mice and perform germline transmission. In this process, genetic and epigenetic factors jointly affect the heterogeneity of ESCs [95]. Similarly, there is heterogeneity in human iPSCs. A large number of studies have shown that genetic background is the biggest factor determining gene expression heterogeneity. In addition, some iPSCs have been proven to have differentiation defects. In neural differentiation, most iPSCs have an efficiency of more than 95% in forming Pax6-positive cells, and a small number have a differentiation efficiency of 80%, while a portion of undifferentiated cells remain [101, 102].

To overcome heterogeneity, researchers have tried to convert the "start" state of hPSCs (human pluripotent stem cells) into the "initial" state. There are many methods reported to induce hPSCs to transform to the initial state, such as using a combination of chemical inhibitors of growth factors, overexpressing NANOG and KLF2 transcription factors, etc [103, 104]. However, this technology may lead to chromosomal abnormalities or loss of imprinting and is still under exploration.

Immunogenicity

Immune rejection has always been an inevitable key issue in cell therapy. The immunogenicity of autologous iPSC is low, but abnormal gene expression may still lead to immune rejection, which has been reported in mouse experiments. In addition, from the perspective of time and price, allogeneic "off-the-shelf" iPSC may be more cost-effective, but this also brings about the problem of immunogenicity.

Some special individuals in the population have a high-frequency haploid homozygous HLA gene 5 locus. Cells from these donors can cover a large number of recipients during cell transplantation. This type of person is also called a "super donor". In response to the immunogenicity problem of "off-the-shelf" iPSC, the establishment of a "super donor" stem cell bank has become a necessary support for development [105]. At present, my country has also established a super stem cell bank that can cover about 14% of the national population; and many companies have also built unique stem cell banks for research and development and screening.

Challenges in stem cell production and preparation

In addition to the challenges that stem cells themselves may bring, there are also corresponding challenges in production and preparation for clinical transformation. Since the proportion of stem cells in the cell population is very low, the markers on their surface are often similar to other types of cells, making it difficult to accurately identify and separate stem cells from complex cell populations. At the same time, there are also challenges in the identification and purification of stem cells. It is still necessary to establish an effective separation, purification, and identification mechanism.

Secondly, In the context of induced pluripotent stem cell (iPSC) production, the process is characterized by its inherent complexity, with uncertainties arising at each stage, including material acquisition, reprogramming, amplification, differentiation, detection, and storage. Given that a significant portion of the raw materials consists of living cells, given that a significant portion of the raw materials consists of living cells, the process necessitates considerable manual intervention, which can result in variability in cell quality. This variability poses significant challenges for Chemistry, Manufacturing, and Controls (CMC) in the future and represents a primary obstacle to the current scaling of production. In response to these challenges, numerous supply chain companies are actively developing equipment designed to facilitate fully automated production, thereby enabling dynamic cultivation and real-time monitoring of stem cells, as well as the acquisition of relevant data more efficiently and stably.

In addition, there are also innovative pharmaceutical companies that continue to make efforts. For example, Alpe Regenerative Medicine has a fully automated, high-scale, industrial-grade cell intelligent manufacturing platform. Its independently innovative and developed fully automated production pipeline can significantly reduce production costs while improving the uniformity and stability of the quality of cell products.

In the domain of stem cell regenerative medicine, the significance of both cell quality and quantity is

paramount, as they collectively ensure the safety and efficacy of therapeutic interventions. However, it is critical to recognize that merely striving for a substantial increase in cell numbers does not inherently guarantee therapeutic effectiveness. Neglecting the fundamental aspect of quality can render even a large quantity of cells ineffective or potentially detrimental to the treatment process. Substandard quality may not only lead to a marked decrease in therapeutic outcomes but can also impose unforeseen stress and burden on the patient's physiology. To navigate this challenge and enhance the standard of medical care, it is essential to rigorously control the quality standards at every stage of stem cell preparation. It is imperative that each stem cell utilized in clinical applications is a meticulously selected and viable progenitor of life. The true therapeutic potential can only be realized by harmonizing high quality with an appropriate quantity, which reflects a responsible approach towards patient care and serves as a critical indicator of advancements in medical science. Factors influencing the dosage of stem cells include their proliferation and division capabilities, culture generation, serum composition, and the environmental conditions of the culture medium.

Conclusion

As an emerging treatment technology, stem cells are complex and specific, and more clinical data are still needed to verify their clinical efficacy. In terms of supervision, different countries have explored and formulated corresponding regulatory policies based on their own research foundations and development concepts, and they are still in the process of continuous improvement. We have reviewed the fields of stem cell therapy by 2024, covering multiple medical fields such as anti-aging, plastic surgery and repair, cardiovascular disease, autoimmune diseases, etc., and also involve specific clinical applications and research priorities. The potential and application value of stem cell therapy have been fully affirmed and prospected. As a cell with the potential for self-renewal and multidirectional differentiation, stem cells provide new treatment strategies for many intractable diseases. With the deepening of research and technological advancement, we have reason to believe that stem cell therapy will play an increasingly important role in the future medical field.

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Declarations
The authors declare that they have not use AI-generated work in this manuscript.

Author contributions
Chen Fu, Fengfeng Li conceived, designed, and revised the manuscript; Chen Fu wrote and revised the manuscript; Fengfeng Li revised the manuscript and discussed interpretation. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Data availability
Not applicable, all information in this review can be found in the reference list.

Declarations

Ethics approval and consent to participate
No ethics approval was required for this review that did not involve patients or patient data.

Consent for publication
All authors approved this manuscript for publication.

Competing interests
The authors declare no competing interests.

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References

1. Segunda MN, Diaz C, Torres CG, Parraguez VH, De Los Reyes M, Peralta OA. Comparative analysis of the potential for germ cell (GC) differentiation of bovine peripheral blood Derived-Mesenchymal stem cells (PB-MSC) and spermatogonial stem cells (SSC) in Co-Culture system with Sertoli cells (SC). Anim (Basel) 2023, 13.
2. Cancedda R, Mastrogiacomo M. The Phoenix of stem cells: pluripotent cells in adult tissues and peripheral blood. Front Bioeng Biotechnol. 2024;12:1414156.
3. Hong YJ, Hong K, Byun S, Choi HW, Do JT. Reprogramming of extraembryonic trophoblast stem cells into embryonic pluripotent state by fusion with embryonic stem cells. Stem Cells Dev. 2018;27:1350–9.
4. Wei TT, Chandy M, Nishiga M, Zhang A, Kumar KK, Thomas D, Manhas A, Rhee S, Justesen JM, Chen IY, et al. Cannabinoid receptor 1 antagonist genistein attenuates marijuana-induced vascular inflammation. Cell. 2022;185:1676–e16931623.
5. Ratajczak MZ, Liu R, Marlicz W, Blogowski W, Starzynska T, Wojakowski W, Zuba-Surma E. Identification of very small embryonic/epiblast-like stem cells (VSELs) Circulating in peripheral blood during organ/tissue injuries. Methods Cell Biol. 2011;103:31–54.
6. Ma S, Jiang Y, Qian Y, Du J, Yu X, Luo S, Chen Z. The emerging biological functions of exosomes from dental Tissue-Derived mesenchymal stem cells. Cell Reprogram. 2023;25:53–64.
7. Katayama M, Fukuda T, Kaneko T, Nakagawa Y, Tajima A, Naito M, Ohmaki H, Endo D, Asano M, Nagamine T, et al. Induced pluripotent stem cells of endangered avian species. Commun Biol. 2022;5:1049.
8. Vallabhaneni H, Shah T, Shah P, Hursh DA. Suspension culture on microcarriers and as aggregates enables expansion and differentiation of pluripotent stem cells (PSCs). Cytotherapy. 2023;25:993–1005.
9. Isono W, Kawasaki T, Ichida JK, Nagasaka K, Hiraike O, Umezawa A, Akutsu H. Transcriptomic analysis of feeder-free culture system for maintaining naive-state pluripotency in human pluripotent stem cells. Stem Cell Investig. 2023;10:10.
10. Alanazi RF, Alhwity BS, Almahlawi RM, Alatawi BD, Albalawi SA, Albalawi RA, Albalawi AA, Abdel-Maksoud MS, Elsherbiny N. Multilineage differentiating stress enduring (Muse) cells: A new era of stem Cell-Based therapy. Cells 2023, 12.

11. Guo Y, Yang LL, Qi HY. Transcriptome analysis of mouse male germline stem cells reveals characteristics of mature spermatogonial stem cells. Yi Chuan. 2022;44:591–608.
12. Bahmad HF, Elajami MK, Daouk R, Jalloul H, Darwish B, Chalhoub RM, Assi S, Chamaa F, Abou-Kheir W. Stem cells: in sickness and in health. Curr Stem Cell Res Ther. 2021;16:262–76.
13. Vasuri F, Fittipaldi S, Pasquinelli G. Arterial calcification: Finger-pointing at resident and Circulating stem cells. World J Stem Cells. 2014;6:540–51.
14. Maehle AH. Ambiguous cells: the emergence of the stem cell concept in the nineteenth and twentieth centuries. Notes Rec R Soc Lond. 2011;65:359–78.
15. Hossfeld U, Levit GS, Watts E. 100 years of phenogenetics: Valentin Haecker and his examination of the phenotype. Mol Genet Genomics. 2019;294:445–56.
16. Hossfeld U, Watts E, Levit GS. Valentin Haecker (1864–1927) as a pioneer of phenogenetics: Building the Bridge between genotype and phenotype. Epigenetics. 2017;12:247–53.
17. Cieri N, Maurer K, Wu CJ. 60 years young: the evolving role of allogeneic hematopoietic stem cell transplantation in cancer immunotherapy. Cancer Res. 2021;81:4373–84.
18. Timofeeva OA, Philogene MC, Zhang QJ. Current donor selection strategies for allogeneic hematopoietic cell transplantation. Hum Immunol. 2022;83:674–86.
19. Lightner AL, Irving PM, Lord GM, Betancourt A. Stem cells and stem Cell-Derived factors for the treatment of inflammatory bowel disease with a particular focus on perianal fistulizing disease: A minireview on future perspectives. BioDrugs. 2024;38:527–39.
20. Chourasiya S, Patel P, Kumar GS, Soni A. A new vision for ocular disease: stem cell strategies in regenerative ophthalmology. Stem Cell Rev Rep 2025.
21. Guida M, Castaldi MA, Rosamilio R, Giudice V, Orio F, Selleri C. Reproductive issues in patients undergoing hematopoietic stem cell transplantation: an update. J Ovarian Res. 2016;9:72.
22. Jansen J. The first successful allogeneic bone-marrow transplant: Georges Mathe. Transfus Med Rev. 2005;19:246–8.
23. Worton RG, McCulloch EA, Till JE. Physical separation of Hemopoietic stem cells differing in their capacity for self-renewal. J Exp Med. 1969;130:91–103.
24. Faltusova K, Bajecny M, Heizer T, Paral P, Chen CL, Szikszai K, Klener P, Necas E. Second bone marrow transplantation into regenerating hematopoiesis enhances reconstitution of immune system. Front Immunol. 2024;15:1405210.
25. Takenaka C, Miyajima H, Yoda Y, Imazato H, Yamamoto T, Gomi S, Ohshima Y, Kagawa K, Sasaki T, Kawamata S. Controlled growth and the maintenance of human pluripotent stem cells by cultivation with defined medium on extracellular Matrix-Coated micropatterned dishes. PLoS ONE. 2015;10:e0129855.
26. Nath SC, Menendez L, Friedrich Ben-Nun I. Overcoming the variability of iPSCs in the manufacturing of Cell-Based therapies. Int J Mol Sci 2023, 24.
27. Fujiwara M, Yan P, Otsuji TG, Narazaki G, Uosaki H, Fukushima H, Kuwahara K, Harada M, Matsuda H, Matsuoka S, et al. Induction and enhancement of cardiac cell differentiation from mouse and human induced pluripotent stem cells with cyclosporin-A. PLoS ONE. 2011;6:e16734.
28. Hayashi M, Fujihara K, Beder LB, Yamamoto Y, Hotomi M, Yamanaka N. Pathogenic role of tonsillar lymphocytes in associated with HSP60/65 in pustulosis palmaris et plantaris. Auris Nasus Larynx. 2009;36:578–85.
29. Yamanaka Y, Akiyama M, Sugiyama-Nakagiri Y, Sakai K, Goto M, McMillan JR, Ota M, Sawamura D, Shimizu H. Expression of the keratinocyte lipid transporter ABCA12 in developing and reconstituted human epidermis. Am J Pathol. 2007;171:43–52.
30. Veraitch O, Kobayashi T, Imaizumi Y, Akamatsu W, Sasaki T, Yamanaka S, Amagai M, Okano H, Ohyama M. Human induced pluripotent stem cell-derived ectodermal precursor cells contribute to hair follicle morphogenesis in vivo. J Invest Dermatol. 2013;133:1479–88.
31. Hirami Y, Osakada F, Takahashi K, Okita K, Yamanaka S, Ikeda H, Yoshimura N, Takahashi M. Generation of retinal cells from mouse and human induced pluripotent stem cells. Neurosci Lett. 2009;458:126–31.
32. Jin ZB, Okamoto S, Xiang P, Takahashi M. Integration-free induced pluripotent stem cells derived from retinitis pigmentosa patient for disease modeling. Stem Cells Transl Med. 2012;1:503–9.
33. Mandai M, Watanabe A, Kurimoto Y, Hirami Y, Morinaga C, Daimon T, Fujihara M, Akimaru H, Sakai N, Shibata Y, et al. Autologous induced Stem-Cell-Derived retinal cells for macular degeneration. N Engl J Med. 2017;376:1038–46.
34. Okamoto S, Takahashi M. Induction of retinal pigment epithelial cells from monkey iPS cells. Invest Ophthalmol Vis Sci. 2011;52:8785–90.
35. Sugita S, Kamao H, Iwasaki Y, Okamoto S, Hashiguchi T, Iseki K, Hayashi N, Mandai M, Takahashi M. Inhibition of T-cell activation by retinal pigment epithelial cells derived from induced pluripotent stem cells. Invest Ophthalmol Vis Sci. 2015;56:1051–62.
36. Kurtzberg J, Prockop S, Teira P, Bittencourt H, Lewis V, Chan KW, Horn B, Yu L, Talano JA, Nemecek E, et al. Allogeneic human mesenchymal stem cell therapy (remestemcel-L, Prochymal) as a rescue agent for severe refractory acute graft-versus-host disease in pediatric patients. Biol Blood Marrow Transpl. 2014;20:229–35.
37. Patel AN, Genovese J. Potential clinical applications of adult human mesenchymal stem cell (Prochymal(R)) therapy. Stem Cells Cloning. 2011;4:61–72.
38. Prasad VK, Lucas KG, Kleiner GI, Talano JA, Jacobsohn D, Broadwater G, Monroy R, Kurtzberg J. Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. Biol Blood Marrow Transpl. 2011;17:534–41.
39. Lightner AL, Dadgar N, Matyas C, Elliott K, Fulmer C, Khaitan N, Ream J, Nachand D, Steele SR. A phase IB/IIA study of remestemcel-L, an allogeneic bone marrow-derived mesenchymal stem cell product, for the treatment of medically refractory ulcerative colitis: an interim analysis. Colorectal Dis. 2022;24:1358–70.
40. Lightner AL, Ream J, Nachand D, Fulmer C, Regueiro M, Steele SR. Remestemcel-L allogeneic bone marrow-derived mesenchymal stem cell product to treat medically refractory crohn's colitis: preliminary phase IB/IIA study. Br J Surg. 2022;109:653–5.
41. Lim HC, Park YB, Ha CW, Cole BJ, Lee BK, Jeong HJ, Kim MK, Bin SI, Choi CH, Choi CH, et al. Allogeneic umbilical cord Blood-Derived mesenchymal stem cell implantation versus microfracture for Large, Full-Thickness cartilage defects in older patients: A multicenter randomized clinical trial and extended 5-Year clinical Follow-up. Orthop J Sports Med. 2021;9:2325967120973052.
42. Nam JY, Chun S, Lee TY, Seo Y, Kim K, Park J, Sung W, Oh KW, Lee S, Park JS, et al. Long-term survival benefits of intrathecal autologous bone marrow-derived mesenchymal stem cells (Neuronata-R(R): lenzumestrocel) treatment in ALS: Propensity-score-matched control, surveillance study. Front Aging Neurosci. 2023;15:1148444.
43. Nam JY, Lee TY, Kim K, Chun S, Kim MS, Shin JH, Sung JJ, Kim BJ, Kim BJ, Oh KW, et al. Efficacy and safety of Lenzumestrocel (Neuronata-R(R) inj.) in patients with amyotrophic lateral sclerosis (ALSUMMIT study): study protocol for a multicentre, randomized, double-blind, parallel-group, Sham procedure-controlled, phase III trial. Trials. 2022;23:415.
44. Oh KW, Moon C, Kim HY, Oh SI, Park J, Lee JH, Chang IY, Kim KS, Kim SH. Phase I trial of repeated intrathecal autologous bone marrow-derived mesenchymal stromal cells in amyotrophic lateral sclerosis. Stem Cells Transl Med. 2015;4:590–7.
45. Torrents S, Grau-Vorster M, Vives J. Illustrative potency assay examples from approved therapies. Adv Exp Med Biol. 2023;1420:139–49.
46. Cohen JA, Lublin FD, Lock C, Pelletier D, Chitnis T, Mehra M, Gothelf Y, Aricha R, Lindborg S, Lebovits C, et al. Evaluation of neurotrophic factor secreting mesenchymal stem cells in progressive multiple sclerosis. Mult Scler. 2023;29:92–106.
47. Berry JD, Cudkowicz ME, Windebank AJ, Staff NP, Owegi M, Nicholson K, McKenna-Yasek D, Levy YS, Abramov N, Kaspi H, et al. NurOwn, phase 2, randomized, clinical trial in patients with ALS: Safety, clinical, and biomarker results. Neurology. 2019;93:e2294–305.
48. Gothelf Y, Abramov N, Harel A, Offen D. Safety of repeated transplantations of neurotrophic factors-secreting human mesenchymal stromal stem cells. Clin Transl Med. 2014;3:21.
49. Gothelf Y, Kaspi H, Abramov N, Aricha R. MiRNA profiling of NurOwn(R): mesenchymal stem cells secreting neurotrophic factors. Stem Cell Res Ther. 2017;8:249.
50. Kaspi H, Semo J, Abramov N, Dekel C, Lindborg S, Kern R, Lebovits C, Aricha R. MSC-NTF (NurOwn(R)) exosomes: a novel therapeutic modality in the mouse LPS-induced ARDS model. Stem Cell Res Ther. 2021;12:72.
51. Perets N, Segal-Gavish H, Gothelf Y, Barzilay R, Barhum Y, Abramov N, Hertz S, Morozov D, London M, Offen D. Long term beneficial effect of neurotrophic factors-secreting mesenchymal stem cells transplantation in the BTBR mouse model of autism. Behav Brain Res. 2017;331:254–60.
52. Cyranoski D. Stem-cell therapy faces more scrutiny in China. Nature. 2009;459:146–7.
53. Hu L, Zhao B, Wang S. Stem-Cell therapy advances in China. Hum Gene Ther. 2018;29:188–96.

54. Lv J, Su Y, Song L, Gong X, Peng Y. Stem cell 'therapy' advertisements in china: Infodemic, regulations and recommendations. Cell Prolif. 2020;53:e12937.
55. Kwantwi LB, Rosen ST, Querfeld C. The role of signaling lymphocyte activation molecule family receptors in hematologic malignancies. Curr Opin Oncol. 2024;36:449–55.
56. Philippidis A. CASGEVY makes history as FDA approves first CRISPR/Cas9 genome edited therapy. Hum Gene Ther. 2024;35:1–4.
57. Parums DV. Editorial: first regulatory approvals for CRISPR-Cas9 therapeutic gene editing for sickle cell disease and Transfusion-Dependent beta-Thalassemia. Med Sci Monit. 2024;30:e944204.
58. Yang L, Liu SC, Liu YY, Zhu FQ, Xiong MJ, Hu DX, Zhang WJ. Therapeutic role of neural stem cells in neurological diseases. Front Bioeng Biotechnol. 2024;12:1329712.
59. Beghini DG, Kasai-Brunswick TH, Henriques-Pons A. Induced pluripotent stem cells in drug discovery and neurodegenerative disease modelling. Int J Mol Sci 2024, 25.
60. Jankovic J, Okun MS, Kordower JH. Stem cells: scientific and ethical quandaries of a personalized approach to parkinson's disease. Mov Disord. 2020;35:1312–4.
61. Kim MS, Kim H, Lee G. Precision medicine in parkinson's disease using induced pluripotent stem cells. Adv Healthc Mater. 2024;13:e2303041.
62. Albert K, Niskanen J, Kalvala S, Lehtonen S. Utilising induced pluripotent stem cells in neurodegenerative disease research: focus on glia. Int J Mol Sci 2021, 22.
63. Continued Evaluation of Patients With Parkinson's Disease Who. Previously Received BRT-DA01 [https://clinicaltrials.gov/study/NCT05897957?term=BRT-DA01&rank=1]
64. Yan Y, Li Y, Fu Y, Yang L, Su L, Shi K, Li M, Liu Q, Borazanci A, Liu Y, et al. Autoantibody to MOG suggests two distinct clinical subtypes of NMOSD. Sci China Life Sci. 2016;59:1270–81.
65. Zhu W, Zhang Y, Wang Z, Fu Y, Yan Y. Monoclonal Antibody-Based treatments for neuromyelitis Optica spectrum disorders: from bench to bedside. Neurosci Bull. 2020;36:1213–24.
66. Duncan RS, Riordan SM, Gernon MC, Koulen P. Cannabinoids and endocannabinoids as therapeutics for nervous system disorders: preclinical models and clinical studies. Neural Regen Res. 2024;19:788–99.
67. Riordan NH, Morales I, Fernandez G, Allen N, Fearnot NE, Leckrone ME, Markovich DJ, Mansfield D, Avila D, Patel AN, et al. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. J Transl Med. 2018;16:57.
68. Heald AH, Bassett J, Puente-Ruiz N, Clayton P, Stepien KM. Endocrine disorders in adult patients with inherited metabolic diseases: their diagnosis and long-term management. Clin Endocrinol (Oxf) 2024.
69. Luo Y, Ye S, Li X, Lu W. Emerging Structure-Function paradigm of endocrine FGFs in metabolic diseases. Trends Pharmacol Sci. 2019;40:142–53.
70. Annicchiarico A, Barile B, Buccoliero C, Nicchia GP, Brunetti G. Alternative therapeutic strategies in diabetes management. World J Diabetes. 2024;15:1142–61.
71. Maestas MM, Bui MH, Millman JR. Recent progress in modeling and treating diabetes using stem cell-derived Islets. Stem Cells Transl Med 2024.
72. Yun F, Zhaorigen B, Han X, Li X, Yun S. Islet like cells induced from umbilical cord mesenchymal stem cells with neonatal bovine pancreatic mesenchymal exosomes for treatment of diabetes mellitus. Horm Metab Res. 2024;56:463–70.
73. Tsukamoto M, Kimura K, Yoshida T, Tanaka M, Kuwamura M, Ayabe T, Ishihara G, Watanabe K, Okada M, Iijima M, et al. Generation of canine induced pluripotent stem cells under feeder-free conditions using Sendai virus vector encoding six canine reprogramming factors. Stem Cell Rep. 2024;19:141–57.
74. Safety A. Tolerability, and efficacy study of VX-264 in participants with type 1 diabetes [https://clinicaltrials.gov/study/NCT05791201?term=VX-264&rank=1]
75. Safety A. Tolerability, and efficacy study of VX-880 in participants with type 1 diabetes [https://clinicaltrials.gov/study/NCT04786262?term=VX-880&rank=1]
76. Seixas-Lopes FA, Lopes C, Marques M, Agostinho C, Jardim-Goncalves R. Musculoskeletal Disorder (MSD) Health Data Collection, Personalized Management and Exchange Using Fast Healthcare Interoperability Resources (FHIR). *Sensors (Basel)* 2024, 24.
77. Shchaslyvyi AY, Antonenko SV, Telegeev GD. Comprehensive review of chronic stress pathways and the efficacy of behavioral stress reduction programs (BSRPs) in managing diseases. Int J Environ Res Public Health 2024, 21.
78. Vega A, Martin-Ferrero MA, Del Canto F, Alberca M, Garcia V, Munar A, Orozco L, Soler R, Fuertes JJ, Huguet M, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: A randomized controlled trial. Transplantation. 2015;99:1681–90.
79. Allogenic Adipose Tissue. -Derived Mesenchymal Progenitor Cells for the Treatment of Knee Osteoarthritis [https://clinicaltrials.gov/study/NCT04208646?term=AlloJoin&rank=3
80. Allogenic Adipose-Derived. Mesenchymal Progenitor Cells for the Treatment of Knee Osteoarthritis [https://clinicaltrials.gov/study/NCT06570291?term=AlloJoin&rank=1
81. Mlynarska E, Hajdys J, Czarnik W, Fularski P, Leszto K, Majchrowicz G, Lisinska W, Rysz J, Franczyk B. The role of antioxidants in the therapy of cardiovascular Diseases-A literature review. Nutrients 2024, 16.
82. Jin S, Kang PM. A systematic review on advances in management of oxidative Stress-Associated cardiovascular diseases. Antioxid (Basel) 2024, 13.
83. A Study of iPS. Cell-derived cardiomyocyte spheroids (HS-001) in patients with heart failure (LAPiS Study) (LAPiS) [https://clinicaltrials.gov/study/NCT04945018?term=HS-001&rank=1
84. Epicardial Injection of hiPSC-CMs to Treat Severe. Chronic Ischemic Heart Failure [https://clinicaltrials.gov/study/NCT06340048?term=HiCM-188&rank=1
85. Menasche P. Mesenchymal stromal cell therapy for heart failure: never stop dreaming. J Am Coll Cardiol. 2023;81:864–6.
86. Perin EC, Borow KM, Henry TD, Mendelsohn FO, Miller LW, Swiggum E, Adler ED, Chang DH, Fish RD, Bouchard A, et al. Randomized trial of targeted transendocardial mesenchymal precursor cell therapy in patients with heart failure. J Am Coll Cardiol. 2023;81:849–63.
87. Goetzl EJ, Alpert JS, Chen QM. Human stem cells in regenerative medicine. Am J Med 2024.
88. Li W, Du D, Huang Y, Xu C, Liu Y, Wu X, Yang J, Liu Z, Ma J, Huangfu C. Improvement of skin wound healing by giant salamander skin mucus gel wrapped with bone marrow mesenchymal stem cells via affecting integrin family molecules. Aging. 2024;16:7902–14.
89. Ozhava D, Bektas C, Lee K, Jackson A, Mao Y. Human Mesenchymal Stem Cells on Size-Sorted Gelatin Hydrogel Microparticles Show Enhanced In Vitro Wound Healing Activities. *Gels* 2024, 10.
90. Shanehband N, Naghib SM. Microfluidics-assisted tumor cell separation approaches for clinical applications: an overview on emerging devices. Comb Chem High Throughput Screen 2024.
91. Shi L, Zhou Y, Yin Y, Zhang J, Chen K, Liu S, Chen P, Jiang H, Liu J, Wu Y. Advancing tissue damage repair in geriatric diseases: prospects of combining stem Cell-Derived exosomes with hydrogels. Int J Nanomed. 2024;19:3773–804.
92. Stem Cells Market Size. Share & Trends Analysis Report By Product (Adult Stem Cells, Human Embryonic Stem Cells), By Application (Regenerative Medicine, Drug Discovery & Development), By Technology, Therapy, By End-use, By Region, And Segment Forecasts, 2024–2030 [https://www.grandviewresearch.com/industry-analysis/stem-cells-market
93. Xu J, Ou J, McHugh KP, Borys MC, Khetan A. Upstream cell culture process characterization and in-process control strategy development at pandemic speed. MAbs. 2022;14:2060724.
94. Pluripotent stem cell. expansion and scale-up [https://www.cytivalifesciences.com/en/us/solutions/emerging-biotech/knowledge-center/upstream-processing-stem-cells
95. Kinney MA, Vo LT, Frame JM, Barragan J, Conway AJ, Li S, Wong KK, Collins JJ, Cahan P, North TE, et al. A systems biology pipeline identifies regulatory networks for stem cell engineering. Nat Biotechnol. 2019;37:810–8.
96. Smulders PSH, Heikamp K, Hermanides J, Hollmann MW, Ten Hoope W, Weber NC. Chemotherapy-induced peripheral neuropathy models constructed from human induced pluripotent stem cells and directly converted cells: a systematic review. Pain. 2024;165:1914–25.
97. Satheka AC. Upscaling of Clinical Grade Stem Cell Production: Upstream Processing (USP) and Downstream Processing (DSP) Operations of Cell Expansion, Harvesting, Detachment, Separation, Washing and Concentration Steps, and the Regulatory Requirements. In *Stem Cell Production: Processes, Practices and Regulations.* Edited by Khan FA. Singapore: Springer Singapore; 2022: 159–184.
98. Heywood RM, Marcus HJ, Ryan DJ, Piccirillo SG, Al-Mayhani TM, Watts C. A review of the role of stem cells in the development and treatment of glioma. Acta Neurochir (Wien). 2012;154:951–69. discussion 969.
99. Kondoh H. Molecular basis of cell reprogramming into iPSCs with exogenous transcription factors. Results Probl Cell Differ. 2024;72:193–218.

100. Nishiga M, Qi LS, Wu JC. CRISPRi/a screening with human iPSCs. Methods Mol Biol. 2021;2320:261–81.
101. Shiraki N, Maruyama K, Hayashi R, Oguchi A, Murakawa Y, Katayama T, Takigawa T, Sakimoto S, Quantock AJ, Tsujikawa M, Nishida K. PAX6-positive microglia evolve locally in hiPSC-derived ocular organoids. Stem Cell Rep. 2022;17:221–30.
102. Neaverson A, Andersson MHL, Arshad OA, Foulser L, Goodwin-Trotman M, Hunter A, Newman B, Patel M, Roth C, Thwaites T, et al. Differentiation of human induced pluripotent stem cells into cortical neural stem cells. Front Cell Dev Biol. 2022;10:1023340.
103. De Los Angeles A, Sakurai M, Wu J. Embryonic chimeras with human pluripotent stem cells. Methods Mol Biol. 2019;2005:125–51.
104. Gong Z, Shu Z, Zhou Y, Chen Y, Zhu H. KLF2 regulates stemness of human mesenchymal stem cells by targeting FGFR3. Biotech Histochem. 2023;98:447–55.
105. Majumder P, Lee JT, Rahmberg AR, Kumar G, Mi T, Scharer CD, Boss JM. A super enhancer controls expression and chromatin architecture within the MHC class II locus. J Exp Med 2020, 217.

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