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Review Article

# A Comprehensive Review of Stem Cells and Applications in Specific Diseases and Regenerative Therapy

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## Abstract

Stem cells (SCs) are undifferentiated progenitor cells present in multicellular organisms. They have the remarkable capacity to proliferate and differentiate into a wide range of various types of specialized cells. SC treatment has emerged as a intriguing research topic and opportunity for new therapies. The phenomenal breakthrough in SC research has provided the groundwork for cell-based therapeutics for diseases that traditional drugs cannot manage, such as ophthalmic disorders. Excellent outcomes have also been achieved in managing potential chronic medical diseases, such as diabetes and cardiomyopathy. SCs represent the frontiers of tissue regeneration due to their capacity for self-renewal and ability to develop into various types of cells. Clinical studies involving SC-based therapeutics have advanced at an exponential rate in recent years. Since their discovery, improvements in SC research have been irregular; and many issues restrict their utility. Nonetheless, breakthroughs have occurred in understanding their molecular genetics. These challenges concern not just tumor development in animal studies and transplant rejection, but also ethical and social considerations surrounding the use of embryonic cells. This comprehensive review of the history of SC research includes notable milestones that have been achieved in the growth of this crucial field of biomedicine.

***Keywords:*** *Stem Cells (SCs); Specific Diseases; Regenerative Therapy*

## Introduction

Stem cells (SCs) are undifferentiated cells in the human body that can self-renew and can transform into any cell in the body. This ability enables SCs to perform various jobs, one of which serves as an internal repair mechanism. Also, their propensity to divide indefinitely can assist in replacing particular cell types and tissues [1–3].

The term Stem Cell was coined by evolutionary biologists Theodor Heinrich Boveri (1862-1915) and Valentin Häcker (1864–1927) to characterize cells devoted to giving birth to the germline. Boveri discovered that some cells might rejuvenate with subsequent functional specialization during his cytology and genetic manipulation experiment. On this premise, he believed that tumor cells began with a cell that had been disrupted by its chromosomes, resulting in an abnormally dividing cell [4].

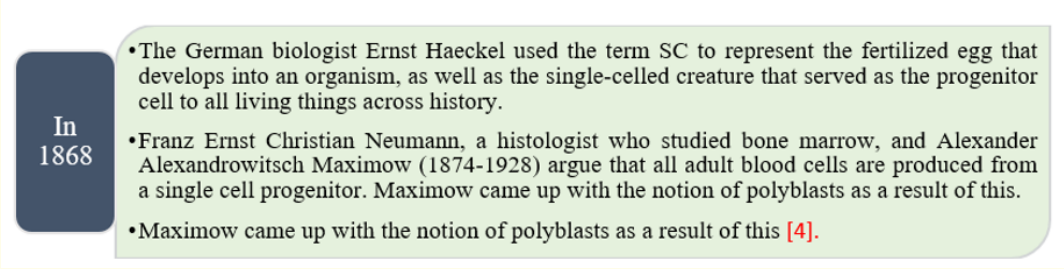


***Figure A***

Ernst Haeckel (1834–1919) later coined the term "SCs" to describe these cells that can regenerate and differentiate [4].

In 1932, Dr. Florence Sabin discovered undifferentiated hematopoietic SCs (HSC) in the bone marrow. Later in the 1950's, Dr. Thomas of the Fred Hutchinson Cancer Research Center began his research on bone marrow transplantation, proving the presence of HSCs. In the late 1950s, he was the first to perform an effective bone marrow transplant to treat a malignancy in conjoined twins, one of whom had leukemia. Because both share an identical genetic composition, no complications with the transplant were observed [2].

Ernest Armstrong McCulloch (1926–2011), a biophysicist, and James Edgar Till, a cell biologist, were innovators using the quantitative clonal approach to examine SCs in the early 1960s. They discovered tumors in the spleen after injecting the cells into the bone marrow of previously irradiated lab mice. All of these cell colonies were derived from a single progenitor cell [5]. With the help of the molecular scientist Lou Siminovitch (born in 1920), they later realized that cells could effectively self-renew by forming clusters [6]. In 1958, Georges Mathé conducted the first effective allogeneic bone marrow transplant in genetically unrelated patients, and in 1963 he cured a patient with leukemia using a bone marrow transplant [4].

The detection of HSC in human cord blood was the next significant breakthrough in 1978. Martin Evans and Matthew Kaufman collected mouse embryonic SCs (ESC) from mouse blastocysts not long after—resulting in the first mouse ESC discovery and the first *in vitro* SC line established from mice. Gail R. Martin demonstrated many strategies for collecting mouse ESCs almost concurrently in the same year. She showed that ESCs are pluripotent by witnessing a wide range of cell types generated with single isolated cells. She is credited with coining the term "ESC" [4].

In 1997, two significant discoveries occurred. First, Bonnet and Dick showed that leukemia is derived from an HSC. Secondly in 1997, the first artificial animal clone, Dolly the sheep, was created by transferring the nucleus of an adult cell into an unfertilized egg that had its nucleus extracted. Then, this new cell was electrically shocked and vivified to proliferate. Finally, it was placed in a surrogate mother once it matured into a blastocyst [2].

**Note**

- Dolly's creation demonstrated that genes in the nucleus of a mature differentiated somatic cell are capable of returning to an embryonic totipotent state, resulting in a cell capable of developing into any component of an animal [2].

***Figure B***

James Alexander Thomson, found ESCs in his 1998 study. In 2007, he developed the technology of human-induced pluripotent SCs (iPS), which involves turning skin cells into cells that closely match human ESCs [7,8]. In 2001, the first investigation of umbilical cord SC transplantation in individuals was reported. In 2004, Gesine Koegler and colleagues discovered pluripotent SCs in the umbilical cord blood in addition to HSCs [9].

**In 2012**

- Shinya Yamanaka and John Gurdon received the Nobel Prize in Physiology or Medicine for discovering that mature cells may be transformed to SCs and can be modified to become pluripotent [10].

***Figure C***

## Discussion

### Stem cell classification

SCs are classified into five broad types based on their origin: the embryo, fetus, infant induced pluripotent SCs, or adults. They may be further classified according to distinctions, such as totipotent, pluripotent, multipotent, oligopotent, or unipotent [11,12] (Figure 1).

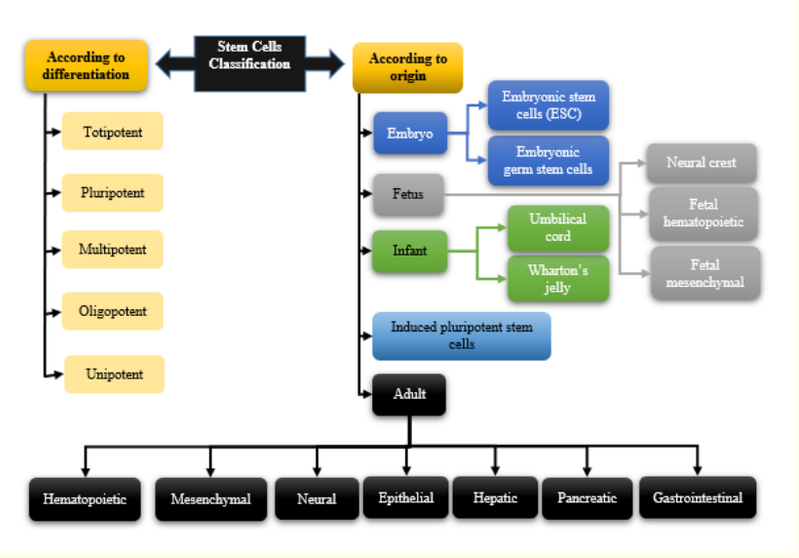


***Figure 1:*** *Classification of stem cells.*

## Stem cells as an adjuvant in the medical treatment of specific conditions

SCs have significant potential to treat a multitude of diseases due to their ability to restore, regenerate, and grow into a variety of specialized cell types [3]. SC transplantation has been used to treat over 100 different illnesses. Figure 2 depicts some of the ways SCs are used as an adjuvant in medical care [4,13].

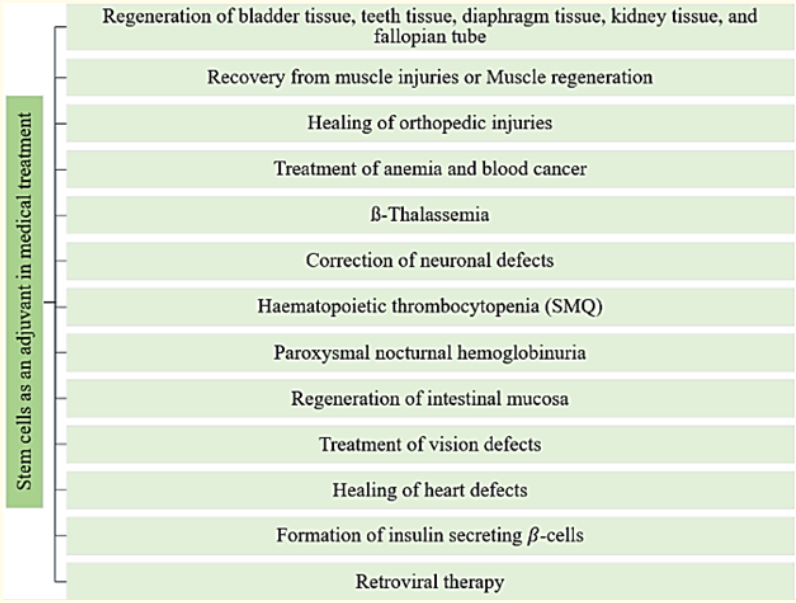


***Figure 2:*** *Stem cells as an adjuvant in medical treatment.*

## Stem cells biology, differentiation, and unique pluripotency

SCs exist in both embryos and adult cells [3]. They play an essential role in tissue development and healing [11]. Because they can reproduce themselves by asymmetric cell division, they can create offspring cells that retain the characteristics of the mother cell, which has a varied efficacy and ancestry potential, such as a committed parent that transiently amplifies to produce many progeny [12].

The SC differentiation process involves changing from proliferation to specialization, transforming a cell into a more specialized cell type. This transformation is accomplished by changing cell shape, membrane potential, biochemical processes, and signal receptivity. Differentiation results in a cell's commitment to developmental lineages and the acquisition of specialized activities by committed cells, which differ depending upon the final recipient tissue. Signaling mechanisms and changes in gene expression play a significant role in SC development. SCs may be divided into five types based on their ability to differentiate, as illustrated in Figure 1 [11–15]. Totipotent SC can differentiate into all varieties of cells. Pluripotent SCs can evolve into all types of cells, except cells of the embryonic membrane. Multipotent SC can differentiate into a limited variety of cell types. Unipotent SCs can self-renew and develop into a single lineage. Oligopotent SCs can divide and self-renew but do not differentiate [11].

## Stem cells manufacturing standards and culture systems

SC transplants are often products based on human cells or tissue [16]. SCs for integrative clinical trials should be manufactured with appropriate controls to ensure efficacy and reliability [17]. Pharma companies must adhere to globally recognized Good Manufacturing Practice (GMP) requirements. The FDA demands strict safety standards to acquire, prepare, and distribute these items. The FDA in the United States grants authorization to establishments that handle human blood and tissue. In addition, the FDA has designed a system of approved human cell and tissue enterprises. The FDA also issued advisories to clinics regarding the risk presented by unauthorized cellular products that do not adhere to these safety protocols or regulatory standards. SC products must meet the FDA (or similar) and state manufacturing, handling, and facility registration criteria [16].

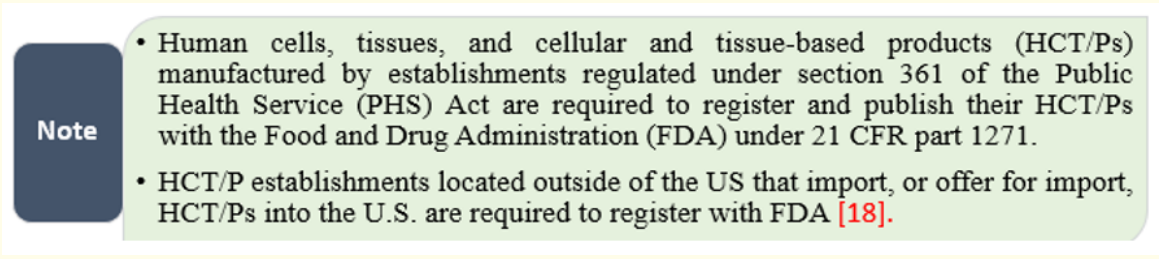


***Figure D***

In contrast, to develop SCs, culture settings must be modified per SC type, e.g. cell culture conditions for ESCs or different types of adult SCs. SC cultures are used for various reasons, such as fundamental research or regenerative treatments. Cell culture conditions are both "instructive" and "supportive" of cell development. SC culture optimization helps create precise non-invasive sensors for online monitoring of crucial parameters, such as pH, $pO_2$, and metabolites. Micro-nanotechnologies—combining microfluidic, multifunctional, and nanomaterials—offer new possibilities to transform traditional cell culture medium into an interconnected bioreactor that closely resembles human anatomy's complexity [19].

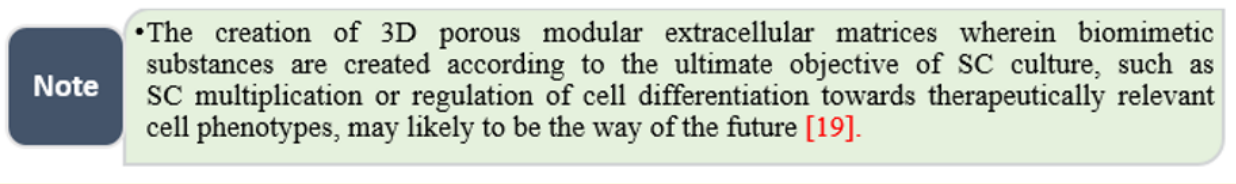


***Figure E***

## Stem cells: Functional division, distinct types, and applications in human therapy

SCs generate new cells through proliferation. These new cells can then divide and develop into specialized cells under the right conditions. SCs may also increase in number without differentiation, causing new SCs, which can replace themselves [20]. The development

of the organism determines the existence of distinct SCs during division. Pre-maturation somatic or adult SCs are undifferentiated and present among differentiated cells throughout the body. The job of these cells is to allow the repair, development, and restoration of cells that are destroyed daily [21]. The differentiation possibilities available to these cells are limited. Figure 3 shows the different types of SC [11,13,22–25].

| Various types of SCs | |
|---|---|
| Neural SC | These cells are found in a few locations of the brain. These cells are capable of giving rise to nerve cells and the cells that support them, such as oligodendrocytes and astrocytes [21]. Neural SC are of two types:<br>• **Endogenous** NSCs, which are found in the hippocampus's dentate gyrus, the sub ventricular zone (SVZ), and the olfactory bulb, and primarily act by producing neurotrophic factors such as NGF and glial cell line-derived neurotrophic factor (GDNF), releasing proangiogenic complexes, regulating the inflammatory environment, and secreting synaptic plasticity-promoting factors such as thrombospondins.<br>• **Exogenous** NSCs: ESCs, iPSCs, bone marrow and adipose-derived MSCs, embryonic NSCs, and stem cells from the fetal and adult neurological systems are all possible sources of exogenous NSCs. These cells can proliferate and develop into neurons, astrocytes, and oligodendrocytes in the presence of numerous growth factors such as EGF, FGF, and leukemia-inhibiting factor (LIF), and may sustain and restore components of the central and peripheral nervous systems [11]. |
| Skin SCs | These cells give rise to keratinocytes, which constitute the skin's protective layer. These cells are also responsible for continuous regeneration of skin as well as healing of wounds. Experts have discovered various kinds of skin SCs so far:<br>• Epidermal SCs: In charge of the daily regeneration of many layers of epidermis. Epidermal SCs are present in the epidermis' basal layer.<br>• Hair follicle SCs: They guarantee that hair follicles are constantly renewed. If the epidermis and sebaceous glands are injured, they can repair them. Hair follicle SCs can be present in all hair follicles.<br>• Melanocyte SCs: they are in charge of the renewal of melanocytes, which are pigment cells [11]. |
| Mesenchymal SCs (MSCs) | • These are the most common SCs found in the human body. They can be found in nearly all tissues, although the most frequent origins are bone marrow, adipose, umbilical cord (UC) tissue, UC blood, and the placenta.<br>• Although MSCs from different tissues have certain similarities, they also have some differences. MSCs, unlike other types of stem cells, are multifunctional; they not only develop into several cell lineages, but they also create a pool of cytokines and growth factors to modulate the immune system, promote damage repair, and tissue regeneration.<br>• MSCs are advantageous for clinical application of SC treatment due to their ability to differentiate into numerous lineages [22]. |
| Hematopoietic SCs (HSC) | • HSCs are a diverse group of cells that generally dwell in bone marrow. HSCs may self-renew and differentiate into all hematopoietic system lineages, including myeloid, lymphoid, megakaryocytic, and erythroid.<br>• These cells give rise to all types of blood cells, including red, white, and platelets. They are in charge of sustaining blood synthesis across our lives [11,21]. |
| Induced pluripotent SCs (IPSC) | • These are mature cells (e.g., epithelial cells) that have been reprogrammed to have pluripotent capabilities. To generate all three germ lines, iPS cells have the ability to self-renew and differentiate indefinitely.<br>• The benefits of employing iPS cells include the ability to generate iPS cells from a patient's personal somatic cells without raising ethical concerns.<br>• While the risk of iPS cell rejection has been demonstrated to be low when supplied to the same individual, it has been noted that the immunogenicity of iPS cells may vary due to fatal mistakes or mutations during the reprogramming and differentiation processes [11,23]. |
| Embryonic SCs (ESC) | • ESCs are generated from the blastocyst's inner cell mass. ESCs are pluripotent, which means they have the ability to develop into all cell types of the organism in vitro given certain culture conditions, as well as indefinite self-renewal and growth.<br>• ESCs give rise to all descendants of the three basic germ layers throughout development: ectoderm, endoderm, and mesoderm. They have no effect on the extra-embryonic membranes or the placenta [11,23]. |
| Umbilical cord SCs (UCSCs) | • The umbilical cord, which is usually thrown away after a child is born, is the most well-known source of SCs since it is obtained in a noninvasive method and has less ethical limitations than ESCs. [11]<br>• The umbilical cord is a major source of HSCs and MSCs, both of which have tremendous regeneration potential. Cord blood HSCs are responsible for the continuous regeneration of all types of blood cells as well as protective immune cells [13] |
| Tissue specific progenitor SCs (TSPSCs) | • These cells, which may be found in a variety of adult organs, help to maintain tissue regeneration and repair following damage. They have the ability to develop into various tissue cells.<br>• Inner ear stem cells can be transformed into auditory hair cells, skin progenitors can become vascular smooth muscle cells, mesoangioblasts can become tibialis anterior muscles, and dental pulp stem cells can become serotonin cells, thanks to cell growth and transformation factors secreted by TSPSCs [13,24] |
| Bone marrow SCs (BMSCs) | • Bone marrow, which is found in soft spongy bones, is responsible for the creation of all peripheral blood and is made up of hematopoietic stem cells (those that produce blood cells) and stromal cells [13].<br>• These cells can develop into other mesodermally related tissues, such as skeletal or heart muscle [25].<br>• BMSCs can rebuild craniofacial, brain, diaphragm, and liver tissue, as well as reinstate erectile function and transdifferentiate monocytes. These multipotent stem cells have the potential to heal the host of cancer as well as HIV and HCV infection [13]. |

***Figure 3:*** *Distinct SC types.*

Due to their vast therapeutic potential, these different SC types—that come from various and distinct loci in the body—can be used in research and to treat many diseases (such as cardiovascular, endocrinological, immunological, pulmonary, respiratory, gastrointestinal, digestive, neurological, dermatological, orthopedic, and dental) (Figure 4) [13].

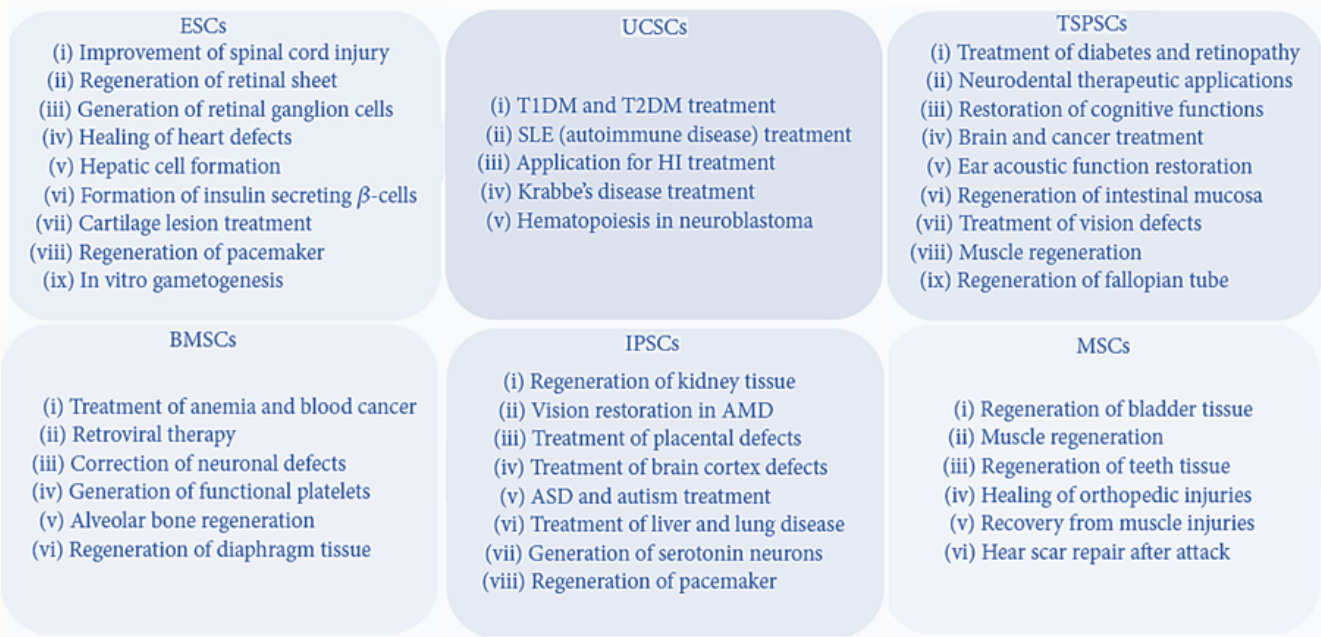


***Figure 4:*** *Stem cell potential in medicine; the six classes of stem cells: ESCs, TSPSCs, MSCs, UCSCs, BMSCs, and iPSCs—have significant beneficial possibilities in regenerative medicine and disease therapeutics.*

## Stem cells application in the treatment of Human Immunodeficiency Virus (HIV) treatment

HIV infection is a substantial public health problem across the world. Despite this, antiretroviral therapy remains the only therapeutic option. The major drawback of using this therapy is that it does not completely cure the disease and must be used for the rest of one's life. Furthermore, antiretroviral treatment has been associated with several problems and concerns about patient compliance. Thus, the development of a more practical and effective alternative is necessary. SC therapy has demonstrated encouraging results in HIV management in recent years and has the potential to have a significant influence on HIV management and prevention [26–28].

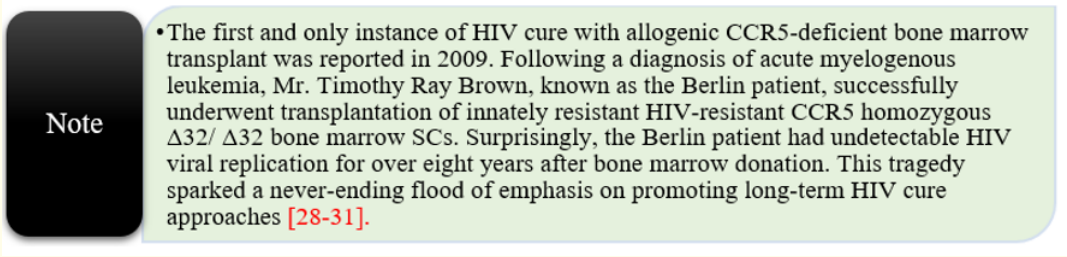


***Figure F***

In the early 1980s, the first SC transplants on HIV+ patients were ignorant about their virus infection. Following these early examples, allogeneic SCT was performed in many HIV+ patients with concurrent malignancy or other hematological disorders worldwide. Figure 5 shows the stages of development of SC-based HIV treatment during the previous decades. After ART became a standard treatment for patients, the effectiveness of this procedure improved significantly [27].

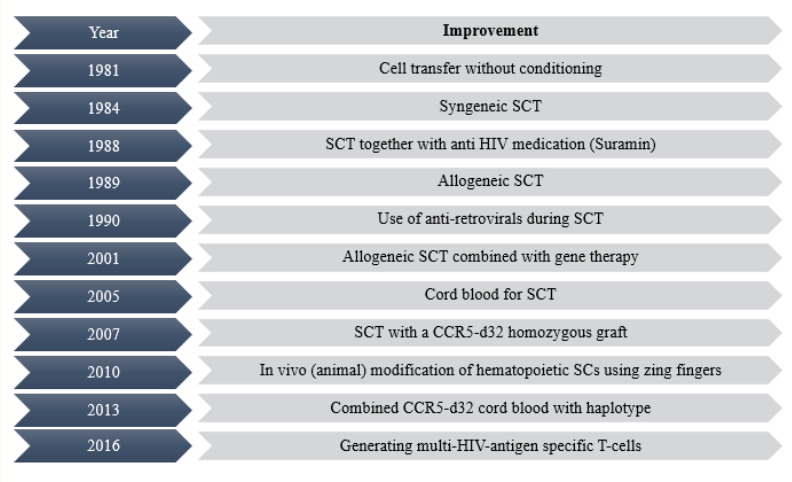


***Figure 5:*** *Advancements in stem cell-based HIV treatment during the recent decades.*

## Stem cells applications in cancer

Cancer is a prominent cause of mortality in high-income and low-income countries, and its medical burden is growing globally as the world's population grows and ages. The most common cancer treatments are surgical resection, fractionated radiation, and chemotherapy. However, many therapeutic alternatives are limited in their efficacy due to treatment-related negative impacts, off-target consequences, and drug resistance [32].

Many research investigations have shown a cellular hierarchy in tumor growth, with a few cells capable of replicating the malignancy through tumor initiation and propagation pathways. In particular, this tiny subset of extremely effective tumor-initiating cells has multipotent SC properties, such as the ability to self-renew and develop. It has been referred to as cancer SCs [33]. In addition, SCs have unique features, such as translocation to tumor cells, the release of bioactive molecules, and immunosuppression, which facilitate tumor targeting and present bypass barriers to gene therapy procedures [32].

SCs, most notably NSCs and MSCs, can be changed through various processes for use in cancer therapy. The therapeutic enzyme-drug system and nanoparticle or oncolytic virus administration to the tumor site are common adaptations. NSCs and MSCs can be genetically designed to amplify enzymes that transform nontoxic intermediates into cytotoxic end products. SCs can behave as in situ drug producers, secreting antitumor drugs for extended periods while overcoming different cancer therapeutic disadvantages, such as high systemic toxicity and shorter drug's half-life [32]. MSC-mediated virus delivery is also a potential strategy for targeted cancer treatment. Ong., *et al*. (2013) revealed that a synthesis of potent oncolytic activity of attenuated measles virus and distinctive immune-privileged and tumor-tropic features of MSCs might attack hepatocellular cancer [34].

## Reprogramming process regarding stem cells

SC reprogramming is when a specialized cell is reverted to a more straightforward form, culminating in cells exhibiting stem-like qualities. This process occurs naturally, mainly for tissue repair and regeneration in old or injured tissues, but can also be generated artificially via gene transcription or chemical substances. Transdifferentiation occurs when specialized cells are transformed effectively into some other type of cell [35].

Takahashi and Yamanaka (2006) investigated the usefulness of specific transcription factors—known to maintain pluripotency in ESCs—for promoting SC pluripotency. The researchers used adult human dermal fibroblasts and cultured them under ESC culture conditions after injecting retroviruses expressing transcription factors Oct3/4, Sox2, Klf4, and c-Myc (OSKM). For the first time, human iPSCs were found to have characteristics comparable to hESCs. They could differentiate into the three embryonic germ layers, allowing the creation of patient-derived cells for cell therapy purposes [36,37].

However, the introduction of retroviruses into cells to transport OSKM is related to concerns concerning genome change. This OSKM-transport was also found to be a time-consuming and inefficient process. However, Huangfu., *et al*. in 2008, tested small compounds for their capacity to boost reprogramming efficiency and discovered that valproic acid could increase OSKM reprogramming efficiency by more than 100-fold [38].

## Stem cell transplantation

SC transplantation (SCT), also known as bone marrow transplantation, is a technique in which a patient is given healthy SC to replace defective SC. To allow the body for transplantation, the patient takes significant doses of chemotherapy and, in some instances, radiation treatment before SCT—referred to as "conditioning therapy." After being injected into the patient's circulation, SCs go to the bone marrow, where they begin the process of creating new healthy blood cells such as WBC, RBC, and platelets—known as "engraftment" [39]. Autologous and allogeneic SC transplantation are the two primary forms of SC transplantation, as shown in figure 6 [40].

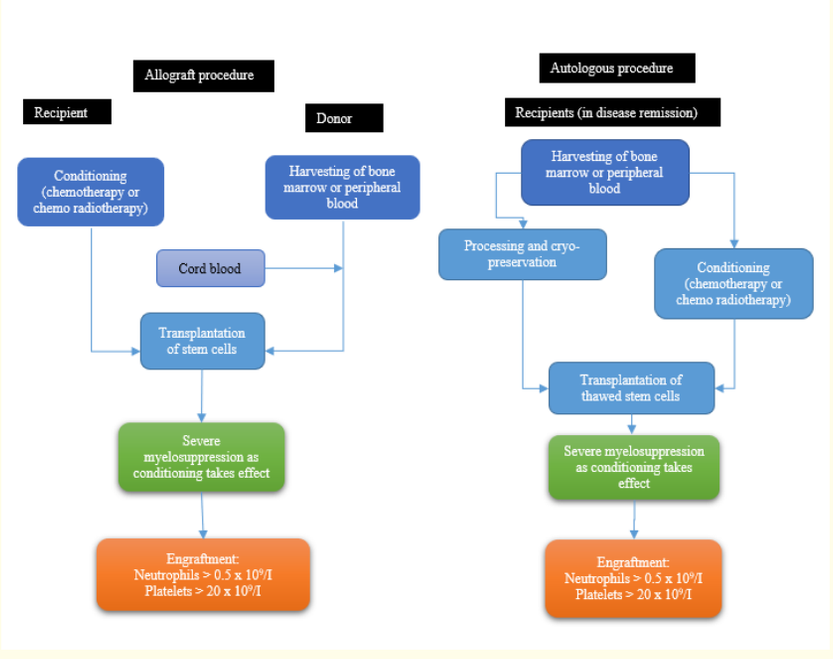


***Figure 6:*** *Stem cell transplantation techniques.*

## Stem cells as a substitute for arthroplasty

Adults over 60 are the most commonly affected by osteoarthritis (OA). Analgesics, NSAIDs, or steroid injections directly into the joint to treat OA. However, many people eventually undergo joint replacement surgery due to decreased mobility or significant pain. SC therapy has developed as a novel and intriguing treatment for osteoarthritic articular cartilage regeneration (OA). For individuals with OA, regenerative cell treatments may offer an alternative to complete joint replacement. Several cell-based therapies employing autologous and allogeneic MSC have been created. In addition, MSCs are being studied as possible treatments for various diseases, including tendonitis, OA, orthopedic trauma, and autoimmune disorders [41]. In the months after administering MSC intra-articularly to OA knees, Freeman., *et al*. (2008) observed less discomfort and improved cartilage density in the joint [42].

Another study by Spasovski., *et al*. (2018) looked at autologous adipose-derived MSCs to manage knee OA. All the researchers reported a substantial decrease in the overall level of VAS pain for everyday activity. After three months, the pain has dropped from an average of 54.5 mm to 20.7 mm. The average score reduced to 9.1 after 18 months post-therapy. In addition, in the first three months, the average flexibility of the patients increased by 17.3° and at six months of follow-up, it increased by 7.8° [43].

## Stem cells in rejuvenation

In humans, aging-related tissue alterations and SC depletion cause tissue homeostasis to be altered, resulting in decreased organ regeneration ability. Various acquired and inherited variables influence the mediation of aging through complicated biological and metabolic mechanisms. Degenerative disorders such as dementia, autoimmune, arthritis, CVD, malignancy, tissue degradation, neuropathy, and obesity are frequently caused by the physiological processes of aging.

Endogenous SCs or exogenous replacement cells produced from the stem or progenitor cells can be used to repair or rejuvenate tissue and maintain homeostasis in SC-based treatments, preventing or decreasing many of these health conditions. Adult SCs, also known as somatic SCs, are self-renewing cell pools that replenish senescent cells and repair damaged tissues throughout the body [44].

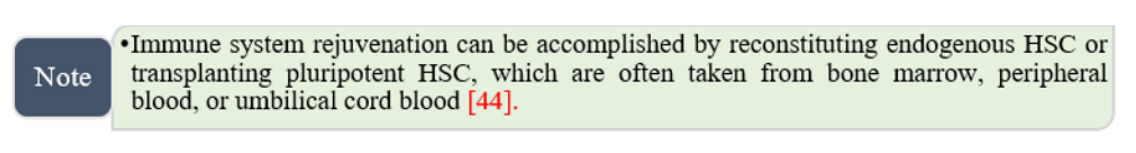


***Figure G***

In 2018, Prakoeswa CRS., *et al*. conducted an 8-week randomized clinical experiment in which 48 women received SC-conditioned amniotic membrane medium (AMSC-CM) or normal saline to treat photo-aged skin. Each patient received three administrations at 2-week intervals following micro-needling to increase epidermal penetration. Statistically, AMSC-CM induced massive improvements in clinical measurements of pores and wrinkles, polarized spots, and spot UV parameters [45].

## Stem cell technology

SC technology is a rapidly evolving field that brings together the efforts of molecular and cellular biology, geneticists, and physicians to offer promise for the successful treatment of a wide range of malignant and non-malignant disorders [46]. For therapeutic purposes,

human SCs have been developed *in vitro* into various cell types: oligodendrocytes, pancreatic cells, cardiomyocytes, and hematopoietic precursor cells [2,47]. Figure 7 lists some of the most recent SC studies that have been published.

| SCs | Disease | Factors causing disease | Mode of stem cells application | Physiological and mechanistic aspects of SC therapeutics | Improvements in disease signatures & future use |
|---|---|---|---|---|---|
| **ESCs** | Spinal cord injuries | Infection, cancer, and accidents | ESCs transplantation to injury site | ESCs and secreted vasculogenic and neurogenic factor support tissue homing | Regeneration of spinal tissue and improved balance and sensation [48]. |
| | Osteoarthritis | When cartilage tissue wears away | Transplantation of chondrocytes organoids | Chondrocytes (SOX9+ & collagen-II+) form cell aggregates remain active for 12wks at transplantation site | Regeneration of cartilage tissue can be used for treatment of injuries faced by athletes [49]. |
| **TSPSCs** | Acoustic problems | Age, noise, drugs, and Infection | IESCs/IESCs-derived hair cells transplantation | $\gamma$-secretase inhibits notch by $\beta$-catenin & Atoh1 activation in lrg5+IESCs to regenerate cochlear cells | Cochlear regeneration leads to restoration of acoustic functions[50,51]. |
| | Eye disease & retinopathy | Toxins, burns, and genetic factors | AdSCs intravitreal transplantation | AdSCs from healthy donor produce higher vasoprotective factors | Restoration of vascularisation, diabetic retinopathy treatment [52,53]. |
| **MSCs** | Alopecia | Age, disease, and medicine use | Transplantation of GAG-coated DPCs | GAG coating mimics ECM microenvironment, promoting DPCs regeneration | Regeneration of hair follicle for treatment of alopecia [54,55]. |
| | Muscle degeneration | Genetic factors and work stress | Coaxed MSCs transplant and MSCs infusion | Alginate gel protects MSCs from immune attack and controls GFs release | Regeneration of heart scar and muscle tissue in controlled way [56]. |
| **iPSCs** | Lung degeneration | Tuberculosis, cancer, and fibrosis | Biomaterial coaxed iPSCs transplantation | Miniature iPSCs lung resembles airways and alveoli, model drug testing | Regeneration of lung tissue [57]. |
| **BMSCs** | Orodental deformities | Trauma, disease, and birth defects | Bone marrow derived stem & progenitor (TRC) | CD14+ & CD90+ TRC accelerate alveolar jaw bone regeneration | Regeneration of defects in oral bone, skin, and gum [58]. |

***Figure 7:*** *Clinical application of stem cells in various diseases.*

## Stem cells storage and preservation

Storage or preservation of SC is essential for both diagnostic and therapeutic applications of SC therapies. The ability to store cells allows the fulfillment of product safety screening before use and the transit of cells between the collection, processing, and clinical administration [59]. SC storage processes are explained in Figure 8 [59–61].

## Moral considerations and ethical issues, and controversies regarding the medical use of stem cells

SC research is tied to ethical and moral concerns that have been raised throughout the world. The most significant recurring problem is the ethical dilemma concerning the use of ESCs. ESCs are significantly superior in potency; unfortunately, their generation necessitates

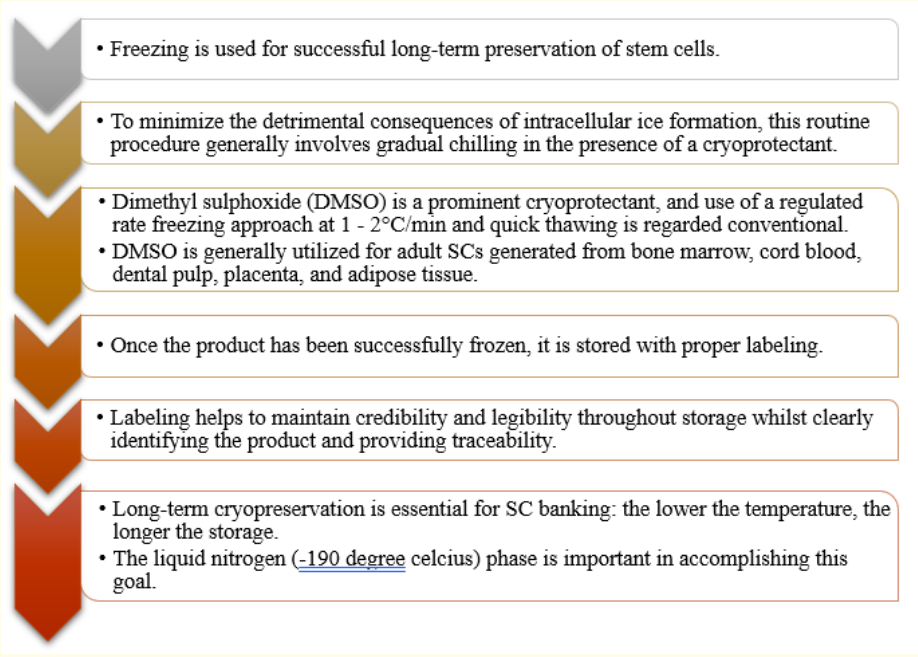


***Figure 8:*** *Stem cell storage or banking process.*

the killing of embryos. The discovery of iPSCs alleviated this issue; nevertheless, iPSCs themselves are currently involved in an ethical debate, addressing their endless differentiation ability and concerns that these cells may one day be used in human cloning [62].

There are two critical associated concerns for stem cells separated from the umbilical cord: (a) the acceptable period to obtain donor agreement to use the resultant medical data, and (b) issues with maintenance and cold storage in particular banks. In addition, concerns have been raised about the discomfort and hazards to the provider during the cell isolation procedure when using bone marrow MSCs [63].

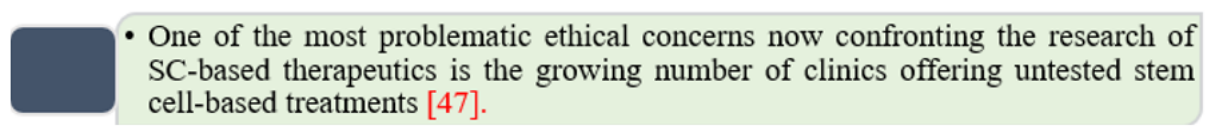


***Figure H***

## Stem cell contraindications regarding their application

All pharmacological interventions have advantages and disadvantages. Likewise, unproven stem cell treatments can sometimes be hazardous. At a 2016 FDA public workshop, panelists discussed multiple stories of serious adverse events due to SC therapy. For example, one patient went blind after receiving an injection of SCs into the eye. Another patient had a spinal cord injection, which developed a

spinal tumor. Therefore, SC therapy is used with caution. Figure 9 illustrates possible contraindications and complications related to SC therapies or transplants [64,65].

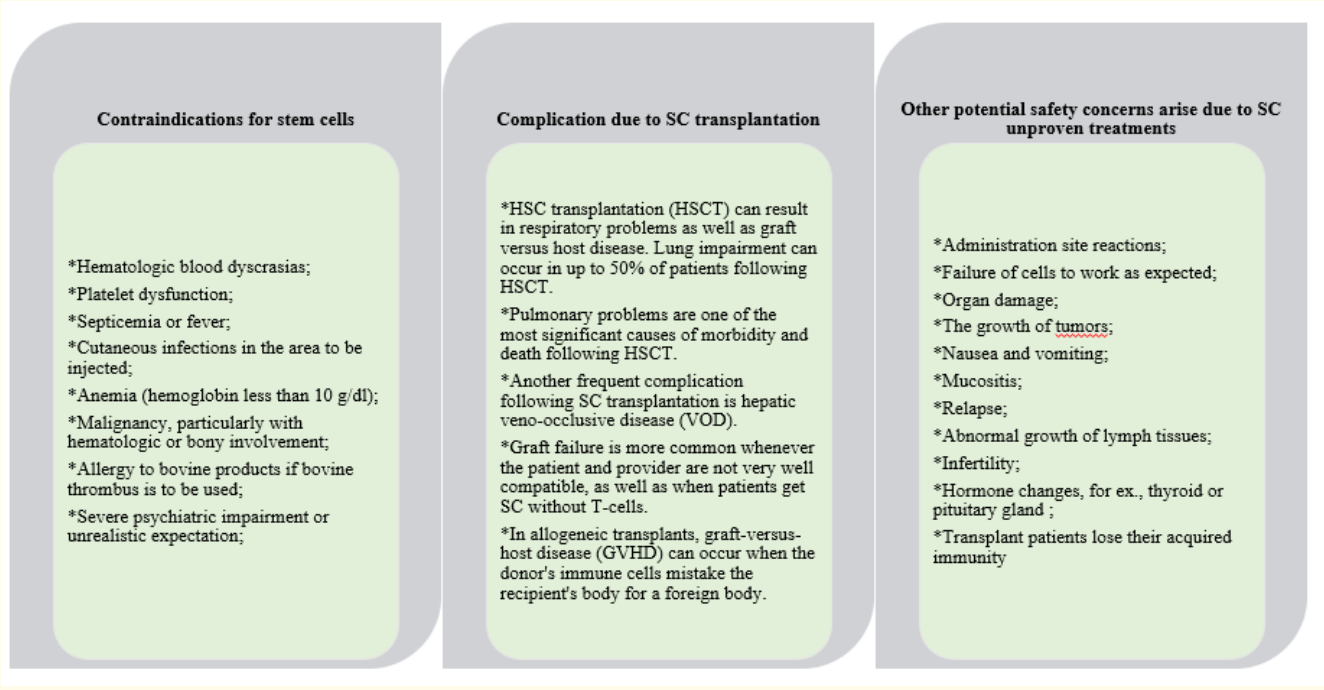


***Figure 9:*** *Possible contraindications and complications related to SC therapies or transplants [65–67].*

## The future of stem cell therapy

In recent years, Therapeutic SC research has moved from using complete SCs to components produced from SCs. SC extracts, microvesicles, and exosomes were among the elements used—each with a different biological activity [22]. The molecular knowledge of SCs will also undoubtedly develop dramatically in the next few years. New approaches will help identify essential genes that govern self-renewal and differentiation in these cells. These could make it possible to modulate SCs *in vivo* beneficially [68]. The quest for and application of a suitable multipotent or pluripotent stem cell in tissue engineering is also a new concept. There may be novel pharmacological substances in the future that can trigger tissue-specific SCs, stimulate SC migration to the side of tissue damage, or encourage SC differentiation to tissue-specific cells [13].

Many aspects of stem cell research and possible clinical applications are, without a doubt, fraught with controversy. In addition, many technological concerns remain unanswered, necessitating strong multidisciplinary partnerships between surgeons, engineers, chemists, and biologists with the ultimate objective of functional tissue repair. However, as more scientific understanding is learned through stem cell research, some of the existing ethical and technological problems will hopefully be addressed or eliminated in the future [69].

## Conclusion

With their restorative, transformational, and invasive abilities, stem cells could conceivably treat any cellular dysfunction disease by replacing those cells. They have the potential to treat tumors more effectively and help patients with chronic disorders—such as stroke, dementia, and diabetes—raising on the prospect of curing diseases previously considered incurable.

Stem cell research regarding various conditions is ongoing—including musculoskeletal ailments, such as muscular dystrophy. However, numerous aspects of stem cell research and potential clinical uses are fraught with controversy and ethical, legal, and social issues. A well-thought-out legislative effort might promote and secure the field's future advancement. Meanwhile, significant efforts are already being made worldwide to establish regulatory rules and standards to ensure patient safety. Furthermore, researchers are now ethically compelled to guarantee that ethical issues are not jeopardized in the quest for clinical translation success. Stem cell-based therapeutics will undoubtedly hold substantial potential as the future of this technology gains more widespread therapeutic usage and acceptance.

## Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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