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## Current Perspectives on Stem Cell Technology in Regenerative Medicine

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### Abstract

Stem cell technology has emerged as a cornerstone of regenerative medicine, offering transformative approaches for the repair, replacement, and regeneration of damaged tissues and organs. This review provides a comprehensive overview of stem cell biology, focusing on the classification, sources, and fundamental properties of stem cells, including embryonic stem cells, adult stem cells, and induced pluripotent stem cells. Current methodologies for stem cell isolation, expansion, differentiation, and delivery are discussed, along with advances in biomaterials, tissue engineering, and gene-editing technologies that enhance therapeutic potential. The clinical applications of stem cell-based therapies in areas such as cardiovascular disease, neurodegenerative disorders, musculoskeletal injuries, and metabolic diseases are critically examined. Additionally, the review addresses key challenges limiting clinical translation, including ethical considerations, immunogenicity, tumorigenicity, and regulatory constraints. By summarizing recent progress and ongoing limitations, this article aims to provide a concise yet comprehensive perspective on the role of stem cell technology in regenerative medicine and its future prospects in clinical practice.

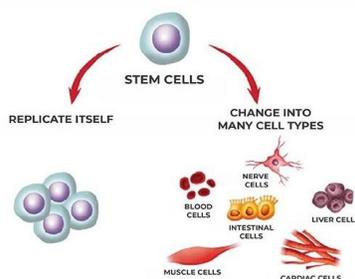
### Keywords

CRISPR-Cas9; Induced pluripotent stem cells; Regenerative medicine; Stem cell therapy; Somatic cell nuclear transfer; Tissue engineering.

## Introduction

Stem cell technology is the core of regenerative medicine, a field aiming to repair, regenerate replace, regenerate or rejuvenate damaged or diseased cells, organs, and tissues to restore normal function. Stem cells, with their unique abilities to self-renew and differentiate into specialized cell types, are used in tissue engineering, cell transplantation, and the development of artificial organs. Applications include treating conditions like heart disease, neurodegenerative disorders, and severe burns by introducing or guiding specialized stem cells to repair injured areas. Human body is formed by 220 stem cell lines, each with unique function. Most become dormant after initial development. Most become dormant after initial development, but stem cell technology and regenerative medicine can i) Repair: fix damaged tissues and restore normal function, ii) Regenerate: grow new healthy cells to replace damaged ones, iii) Replace: substitute old, worn-out cells with fresh ones, and iv) Rejuvenate: restore youthful vitality and energy [1,2].

A stem cell is a blank cell/ precursor cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissues such as a skin, muscle, or nerve cell etc. Stem cells are un-differentiated/ un-specialized/ un-programmed biological cells that are thought to be able to reproduce themselves indefinitely and, under the right conditions to develop into a wide variety of mature cells with specialized functions. They can divide either asymmetrically or mitotically to produce more stem cells. They are found in multicellular organisms (Figure 1). Stem cells possess potential uses in basic research, for clarification of complex events that occur during human development and understanding molecular basis of cancer, molecular mechanisms for gene control, and to provide specific cell types (pluripotent stem cells) to test new drugs, and to reduce animal testing [3].



**Figure 1:** Stem cells can replicate and differentiate into many cell types (Courtesy: VBB Gentek: stem cell types and stem cell therapy).

Regenerative medicine is the broad field focused on repairing, restoring or replacing, or regenerating cells, tissues and organs, to restore normal function. It includes tissue engineering as a method to build tissues externally, and various strategies, including using stem cells, gene therapy, and cell-based therapies to promote the body's natural healing processes internally [4]. Tissue engineering is a specific discipline within regenerative medicine that focuses on growing tissues and organs outside the body. It combines cells (like stem cells), scaffolds (structures to grow cells on), and growth factors to create functional biological tissues. The goal is to replace or restore damaged tissues and organs that can then be implanted into the body [5]. Stem cell therapy is a type of cell-based regenerative medicine that uses stem cells or their derivatives to promote the repair of damaged or diseased tissues. Stem cells, which can differentiate

into specialized cell types, are introduced into the damaged area to help the body heal. The key difference from tissue engineering is that stem cell therapy often works by stimulating the body's innate healing mechanisms rather than by building new tissue from scratch outside the body [2]. In summary, regenerative medicine is the field, tissue engineering is a method within it that involves creating new tissues, and stem cell therapy is another method that uses the body's own cells to initiate healing.

## Stem Cell Therapy

Stem cell therapy is a regenerative treatment that uses the body's own healing cells to promote healing or to repair and restore damaged tissues or diseased organs. Stem cell therapy is introduction of new adult stem cells into damaged tissue in order to treat diseases or injury aiming to regenerate cells (tissue regeneration) to treat various types of tissue damage. These powerful cells can reduce inflammation, support tissue regeneration, and promote natural healing. Also known as regenerative medicine, it aims to replace or regenerate cells, tissues, and organs to treat conditions like cancer, cardiovascular disease, and neurodegenerative disorders. It is commonly used for joint pain, injury recovery, autoimmune conditions, and overall cellular rejuvenation. Any disease in which there is tissue degeneration can be a potential candidate for stem cell therapy: Alzheimer's disease, Parkinson's disease, spinal cord injury, heart disease, severe burns, and diabetes. Stem cells could be used to repair or replace damaged neurons (regenerate spinal cord), repair of damaged organs such as the liver and pancreas [2,4].

Stem cells are sourced (cell sourcing) from various places, including embryonic blastocysts, adult tissues (like bone marrow or fat), umbilical cord blood, and reprogrammed adult cells (iPSCs). Researchers grow these cells in a laboratory (cell cultivation) to produce large quantities for transplantation. Stem cells are then guided to differentiate into specific, functional cell types, such as heart muscle cells, neurons, or blood cells. The specialized cells are implanted (cell implantation) into the patient's damaged or diseased tissue to encourage repair and restoration of function. The transplanted cells need to survive, multiply, and integrate into the host's tissue (tissue integration), receiving nutrients and signaling molecules from the circulatory system to fully participate in regeneration. When stem cells are transplanted into the body and arrive into the injured part, the stem cells come in contact with growth chemicals like EGFs, NGFs and HGFs in the body. These chemicals program the stem cells to differentiate in to the tissue surrounding it [6-8].

Epidermal growth factor (EGF) is a single polypeptide of 53 amino acid residues which is involved in the regulation of cell proliferation. EGF exerts its effects in the target cells by binding to the plasma membrane located protein EGF tyrosine receptor. The EGF receptor is a kinase. Nerve growth factor (NGF) is a neurotrophic factor and neuropeptide primarily involved in the regulation of growth, maintenance, proliferation, and survival of certain target neurons. Hepatocyte growth factor (HGF) is a mesenchyme-derived pleiotropic factor which regulates cell growth, cell motility, and morphogenesis of various types of cells, and is thus considered a humoral mediator of epithelial-mesenchymal interactions responsible for morphogenic tissue interactions during embryonic development [9,10].

In 1968, human adult stem cells were used in the first successful bone marrow transplant. The process includes irradiating the bone marrow to destroy the faulty stem cells (often causing cancer) and replacing

them with normal bone marrow stem cells from a healthy and immune compatible donor. Restoration of blood-forming stem cells after chemotherapy or radiation, a process known as hematopoietic stem cell transplantation is a well-established application in blood and immune disorders. Stem cell transplantation (SCT) is the term now used in preference to bone marrow transplantation (BMT). Today, bone marrow is transplanted routinely to treat a variety of blood and bone marrow diseases, blood cancers, and immune disorders [11].

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Stem cell technology finds applications in regenerative medicine: [12]

- **Cardiac regeneration:** Repairing heart muscle after a heart attack.
- **Neurological conditions:** Replacing damaged neurons in the brain or spinal cord for conditions like Parkinson's, Alzheimer's, and spinal cord injury.
- **Diabetes:** Providing new pancreatic cells to restore insulin production.
- **Wound healing:** Promoting the regeneration of skin tissue in severe burn victims.
- **Oral regeneration:** Regenerating tissues and structures within the mouth.

Stem cell tracking in vivo (in a living organism) uses imaging techniques like optical imaging, magnetic resonance imaging (MRI), and computed tomography (CT) to monitor the location, distribution, and behavior of transplanted cells. Methods involve direct labeling with tracers or indirect methods using reporter genes. Key techniques include bioluminescence and fluorescence for optical tracking, magnetic resonance imaging for high-resolution soft tissue imaging, and computed tomography for tracking with nanoparticles [13].

## Stem Cell Niche

A stem cell "niche" is a specialized microenvironment, both anatomical and functional, that provides the specific signals and support for a stem cell to maintain its identity, regulate its self-renewal, and decide whether to differentiate into new cells. Anatomical location is a specific site within the body where stem cells reside, such as the bone marrow for hematopoietic stem cells. Microenvironment is a complex network of various components that interact to regulate stem cell behavior. The niche includes cell-to-cell interactions (stromal cells and other neighboring differentiated cells), soluble growth factors (cytokines and hormones secreted by niche cells), the extracellular matrix (proteins and other molecules that provide structural support and signaling cues), and even physical factors like oxygen tension, pH, tissue stiffness, and shear stress. In stem cell therapy, understanding and manipulating the niche offers a powerful strategy to enhance stem cell function for tissue repair, by either modifying the in vivo

microenvironment or creating artificial, supportive niches in vitro for transplantation [14].

The stem cell "niche" plays an important role in stem cell therapy by enhancing endogenous healing, improving in vivo function to create artificial in vitro niches in the lab. The stem cell "niche" plays important role in stem cell function by:

1. **Maintaining quiescence:** The niche keeps adult stem cells in a dormant state to prevent exhaustion,
2. **Regulating self-renewal:** It controls the balance between a stem cell dividing to produce another stem cell (self-renewal) and differentiating into a progenitor cell.
3. **Controlling differentiation:** The niche provides signals that direct stem cells to become specific cell types, crucial for tissue development and repair.
4. **Tissue homeostasis:** Niches maintain the normal function of tissues by ensuring a consistent supply of stem cells and their progeny [15].

### **Scaffolds In Stem Cell Based Tissue Engineering**

In stem cell-based tissue engineering, scaffolds serve as a temporary, three-dimensional (3D) structure that mimics the extracellular matrix to guide stem cell growth and organization. They provide mechanical support, facilitate nutrient and waste exchange, and offer a surface for cell attachment, proliferation, and differentiation, ultimately creating new tissue-like structures for repair and regeneration. Scaffolds can also deliver growth factors, drugs, or genes to control the stem cell environment, promoting the development of specific tissues. Scaffolds are used in a variety of tissue engineering applications, including the repair of bone, cartilage, tendons, and ligaments, as well as the regeneration of heart valves and other organs [16,17].

### **Crispr-Cas9 technology enhance stem cell based regenerative medicine**

CRISPR-Cas9 enhances stem cell-based regenerative medicine by enabling precise and efficient genetic modification of stem cells to correct disease-causing mutations, model diseases, or enhance therapeutic properties. It allows for the targeted insertion or deletion of genes, creating genetically engineered stem cells with improved function, reduced immunogenicity, or increased disease resistance, paving the way for novel cell-based therapies. CRISPR-Cas9 is more efficient and specific than older gene-editing technologies, leading to more accurate edits with fewer off-target effects [18].

CRISPR-Cas9 is used to engineer mesenchymal stem cells by generating B2M-knockout mesenchymal stem cells to reduce T-cell differentiation, thereby improving their survival and immunomodulatory effects. CRISPR-Cas9 can create disease models of Parkinson's disease in stem cells, helping researchers understand the disease's progression and develop new treatments. In ex vivo gene-edited cell therapy, hematopoietic stem cells are extracted, corrected using CRISPR, and then reinfused into the patient [18,19].

### **Stem cell characteristics**

Three unique properties of stem cells are i) Self-renewable: Stem cells are capable of dividing and renewing themselves for long periods, ii) Pluripotent: A stem cell is 'uncommitted' until it receives a signal to develop into a specialized cell. Stem cells are unspecialized (blank cells) and can develop into several

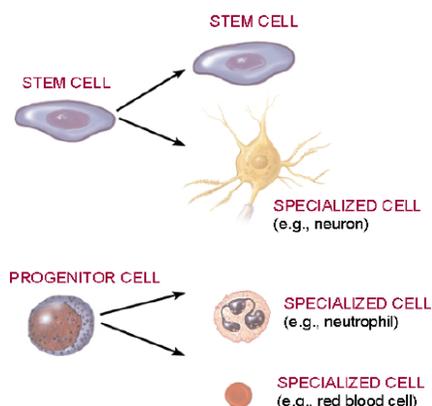
different kinds of specialized cells/tissues, iii) Repair: ability to return to function to damaged cells in the living organism/animal [1-3].

Self-renewal (Regeneration) is the ability of a stem cell to divide and produce copies of itself for an indefinite period of time. The stem cells are capable of dividing and renewing themselves for long periods, whereas somatic cells from adult organs can multiply themselves for a limited number of times. Eventually every adult somatic cell will age and lose its ability to function at peak efficiency, and undergo apoptosis. At this point the dying cell will be replaced from a new cell generated from a local stem cell. When cells replicate themselves many times, it is called proliferation. The stem cells that proliferate for many months in the laboratory can yield millions of cells (Figure 1) [20,21].

Stem cells are defined as unspecialized cells that can renew themselves and differentiate into specialized cell types. A stem cell does not have any tissue-specific structures that allow it to perform specialized functions. A stem cell cannot work with its neighbors to pump blood through the body like a heart muscle cell. It cannot carry molecules of oxygen through the bloodstream like RBC. It cannot fire electrochemical signals to other cells that allow the body to move like a nerve cell [20,21].

Stem cells can give rise to specialized cells. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function i.e. muscle cell, RBC, nerve cell etc. (Figure 1). Stem cells have the ability to divide asymmetrically to produce a differentiated cell and a stem cell. When unspecialized stem cells give rise to specialized cells, the process is called differentiation, in response to external and internal signals. Internal signals are controlled by a cell's genes. External signals include chemicals secreted by other cells (such as growth factors, cytokines), physical contact with neighboring cells, and certain molecules in the microenvironment. Differentiation is the process by which stem cells become specialized to perform particular tasks. Reconstruction of diseased or injured tissue by activation of resident cells or by cell transplantation is known as regenerative medicine. Self-renewal maintains the stem cell pool, whereas differentiation replaces dead or damaged cells throughout life [1,2,20-22].

In embryos, stem cells function to generate new organs and tissues. In adults, they function to replace cells during the natural course of cell turnover. A stem cell is an unspecialized cell that develops into a variety of specialized cell types. A stem cell divides and gives rise to one additional stem cell and a specialized cell e.g., a hematopoietic stem cell undergoing cell division give rise to a stem cell and a blood cell. A progenitor (precursor) cell is unspecialized that is capable of undergoing cell division and yielding two specialized cells e.g., a myeloid progenitor/precursor cell undergoing cell division to yield two specialized cells (a neutrophil and a red blood cell) (Table 1 and Figure 2) [23].



**Figure 2:** Comparison of a progenitor (precursor) cell and a stem cell [23].

Stem cells	Progenitor cells
A stem cell is an unspecialized cell that develops into a variety of specialized cell types	A progenitor is unspecialized that is capable of undergoing cell division and yielding two specialized cells
A stem cell divides and give rise to one additional stem cell and a specialized cell	A progenitor cell divides and gives rise to two specialized cells
e.g., a hematopoietic stem cell produces a second-generation stem cell and a neuron.	e.g., a myeloid progenitor cell undergoing cell division to yield two specialized cells (a neutrophil and a red blood cell)

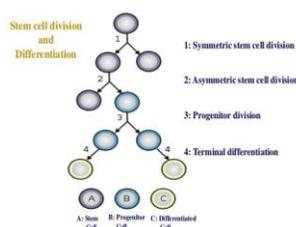
**Table 1:** Comparison of a progenitor (precursor) cell and a stem cell [23].

### Cellular and molecular mechanisms underlying stem cell differentiation and regeneration

Stem cell differentiation and regeneration involve complex molecular and cellular mechanisms, including asymmetric cell division, which balances self-renewal and differentiation by distributing cell fate determinants. Key molecular factors include epigenetic regulators, such as DNA methylation and histone modifications, which control gene expression without changing the DNA sequence. Metabolic shifts from glycolysis to oxidative phosphorylation also influence cell fate, while factors like long non-coding RNAs (lncRNAs) and extracellular vesicles modulate gene expression and cell function to promote regeneration [24].

### Cellular mechanisms

Stem cells divide asymmetrically, placing distinct cell fate determinants into daughter cells, leading to one stem cell and one differentiated cell, ensuring tissue homeostasis (Fig 3). Direct interactions with other cells (cell-cell contact) such as macrophages or endothelial cells can influence stem cell behavior, signaling, promoting differentiation or immunomodulatory effects. Mesenchymal stem cells (MSCs) can transfer mitochondria to damaged cells, improving cellular function and aiding tissue repair. Stem cells release extracellular vesicles, which deliver proteins and RNA to other cells, influencing survival, inflammation, and regeneration [24,25].



**Figure 3:** Stem cell division and differentiation.

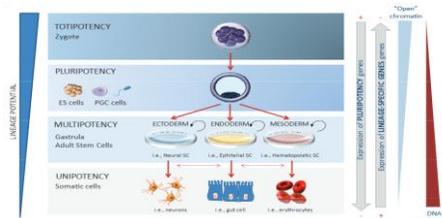
Asymmetric cell division maintains a consistent pool of stem cells to repair and replace damaged or aging cells, a process vital for tissue regeneration and tissue homeostasis. Stem cells, particularly MSCs, can modulate immune responses through secreted factors, direct cell-cell contact, and other mechanisms, creating a supportive environment for tissue repair. Stem cells and their derivatives, like MSCs and EVs, secrete factors that promote tissue reconstruction in wound healing and are explored for treating conditions such as corneal damage [24,25].

### Molecular mechanisms

Mechanisms like DNA methylation and histone modification alter chromatin structure and gene accessibility, playing a critical role in controlling cell fate during differentiation (epigenetic regulation). Stem cell metabolism shifts (metabolic reprogramming) to support different fates; for example, glycolysis is often favored for pluripotency, while oxidative phosphorylation is activated during differentiation into specific lineages. Long non-coding RNA (lncRNA) molecules interact with proteins in the nucleus to regulate gene expression and alternative splicing, shaping transcriptional programs and promoting lineage specification. Secreted growth factors and cytokines, such as those released by mesenchymal stem cells, can promote wound healing, stimulate tissue reconstruction, and exert anti-inflammatory effects. Key signaling pathways regulating stem cell self-renewal include Wnt/ $\beta$ -catenin, Notch, Hedgehog (Hh), Transforming Growth Factor-beta (TGF- $\beta$ ), Fibroblast Growth Factor (FGF), and the JAK-STAT pathway. These pathways control the expression of key transcription factors like OCT4, SOX2, and NANOG, which are essential for maintaining a stem cell's undifferentiated state and its ability to produce more stem cells or differentiate into specialized cells [24,26].

### Classification of stem cells

Adult humans consist of more than 200 kinds of cells. They are nerve cells (neurons), muscle cells (myocytes), skin (epithelial) cells, blood cells (RBC, WBC, platelets), bone cells (osteocytes), and cartilage cells (chondrocytes). Cells essential for embryonic development but not incorporated into the body of embryo, include the extra-embryonic tissues, placenta, umbilical cord. All of these cells are generated from a single, totipotent cell, the zygote, or fertilized egg. The potency of a stem cell is defined by the types of more differentiated cells that the stem cell can make. Based on level of differentiation, stem cells are classified into totipotent, pluripotent, multipotent, oligopotent, and unipotent. Based on source of origin, stem cells are classified into embryonic stem cells and adult stem cells. Embryonic type stem cells include embryonic stem cells and embryonic germ cells, and adult type stem cells include umbilical cord stem cells, placental stem cells, and adult stem cells [27,28].



**Figure 4:** Lineage restriction of human developmental potency [28].

Totipotent stem cells are present in zygote up to morula stage during embryonic development. The fertilized egg is said to be totipotent from the Latin *totus*, meaning “entire”, a cell capable to form all lineages of the entire organism. Totipotent stem cells are the most potent type of stem cell, possessing the unique ability to differentiate into every cell type of an entire organism, including all the cells of the body (embryonic tissues) and the supporting tissues required for development, such as the placenta and fetal membranes (extraembryonic tissues). Found only in the earliest stages of embryonic development, such as the zygote and early blastomeres, these cells represent the highest level of developmental potential before cells begin to specialize. Thus, it has the potential to generate all types of cells and tissues that make up an embryo and placenta, which supports embryonic development in utero. In mammals, only the zygote is totipotent (Figure 4) [28,29].

Pluripotent stem cells (“Pluri” Latin; plures means several or many) are descendants of totipotent stem cells of embryo, develop about four days after fertilization, and can differentiate into any cell type, except for totipotent stem cells and placenta. Pluripotent stem cells only make cells of the embryo proper can make all cells of the embryo (germ cells, cells from any of the germ layers). These cells cannot re-create a complete organism but differentiate to a large number of mature tissue types capable to form all the embryo lineages including germ cells, and some or even all extra-embryonic cell types, for example, brain and muscle. Like embryonic stem cells, these can differentiate into virtually any cell type in the body, offering broad therapeutic potential. An embryo begins as a single, unfertilized egg that divides to form a blastocyst. The blastocyst is made up of embryonic stem cells, which can differentiate into all cells, such as brain, heart, liver and lung cells [28,30].

Pluripotent stem cells are unspecialized cells with the ability to divide indefinitely (self-renew) and differentiate into all cell types of the body, but not extra-embryonic tissues like the placenta. The two main types are embryonic stem cells (ESCs), derived from early embryos, and induced pluripotent stem cells (iPSCs), generated by reprogramming adult cells back to a pluripotent state. These cells are valuable for studying development, drug testing, and developing cell-based therapies for various diseases. Pluripotent stem cells can divide and create more identical cells for long periods in a lab setting. They have the capacity to develop into any of the three primary germ layers (ectoderm, mesoderm, and endoderm), which then give rise to all the specialized cells of the adult body, such as nerve cells, heart muscle cells, and blood cells [28-31].

Multipotent stem cells are descendants of pluripotent stem cells and antecedents of specialized cells in particular tissues, located in every organ of human body. They can differentiate into multiple specialized cells of a closely related family of cells; able form multiple mature cell types that constitute an entire tissue

or tissues. Found in adult organisms and certain tissues like bone marrow, they play crucial roles in tissue repair, regeneration, and homeostasis. They are often found in adult tissues and are considered adult stem cells, but they can also be isolated from other sources like amniotic fluid [28,32].

Multipotent stem cells have a narrower spectrum of differentiation than PSCs, but they can specialize in discrete cells of specific cell lineages. Multipotent stem cells only make cells within a given germ layer. Multipotent stem cells are undifferentiated, self-renewing cells with the ability to develop into a limited range of specific cell types, typically within a single tissue or lineage or embryonic layer in particular. For example, hematopoietic stem cells (also known as blood stem cell), which are found primarily in the bone marrow, give rise to all of the cells found in the blood, including RBCs, WBCs, and platelets (Figure 33.9). Mesenchymal stem cells are found in multiple tissues, including bone marrow, adipose tissue, and umbilical cord blood, and can differentiate into bone cells (osteoblasts), cartilage cells (chondrocytes), fat cells (adipocytes), and myocytes (muscle cells). Neural stem cells are found in the brain, involved in tissue repair and can differentiate into various cell types of the nervous system like neurons, astrocytes, and oligodendrocytes [28,33].

Multipotent stem cells from a mesodermal tissue like the blood can make all the cells of the blood, but cannot make cells of a different germ layer such as neural cells (ectoderm) or liver cells (endoderm). Their ability to regenerate specific tissues makes them valuable for cell-based therapies in treating diseases and injuries, as well as in tissue engineering. Therapeutic potential of multipotent stem cells includes hematopoietic stem cell transplantation, commonly known as bone marrow transplantation, has been used for decades to treat patients with blood-related disorders, such as leukemia, lymphoma, and certain genetic disorders and regenerative medicine [28,33].

Oligopotent stem cells are a type of progenitor cell that can differentiate into a limited number of closely related distinct cell types within a particular lineage e.g., lymphoid cells, but have less differentiation potential than multipotent stem cells. These cells are important for tissue maintenance and repair and have therapeutic potential in regenerative medicine, such as in the generation of specific blood cells from myeloid and lymphoid progenitor cells [27,28].

Unipotent stem cells ('Uni' is derived from Latin word unus, means one) are characterized by the narrowest differentiation capabilities and a special property of dividing repeatedly. Their feature makes them a promising candidate for therapeutic use in regenerative medicine. Unipotent (or progenitor) stem cells are a type of adult stem cell that can differentiate into only one specific type of cell i.e., makes cells of a single cell type e.g., dermatocytes. They are characterized by their limited differentiation potential but possess the crucial ability to self-renew, producing more of their own cell type. Unipotent stem cells are located within specific organs or tissues where they maintain the cell population. An example is a germ cell stem cell that makes the cells that mature to become egg or sperm, but not other cell types. Similarly, erythroid progenitor cells differentiate into only RBCs [27,28].

Unipotent stem cell is a term that is usually applied to a cell in adult organisms, means that the cells in question are capable of differentiating along only one lineage (produce single specific cell type only), but have the property of self-renewal which distinguishes them from non-stem cells e.g., muscle stem cells,

cardiac stem cells, epithelial stem cells. In other words, unipotent stem cells are lineage committed precursor cells (Table 2). Examples include epidermal stem cells found in the skin and can only differentiate into new skin cells, spermatogonia stem cells found in male testes, responsible for producing sperm cells, myoblasts are unipotent cells in muscle tissue that can only form new muscle cells, and cardiomyocytes found in the heart, that only produce more heart muscle cells [27,28].

Unipotent stem cells play a crucial role in maintaining bodily functions by constantly replenishing specialized cells. They are essential for the continuous ongoing regeneration and repair processes in tissues that require a steady supply of a particular cell type [27,28].

<b>Totipotent</b>	<b>Pluripotent</b>	<b>Multipotent</b>	<b>Unipotent</b>
Cells from early embryo	Cells from blastocyst	Fetal tissue, cord blood and adult stem cell	Adult cells
Able to become whole individual including extraembryonic structures i.e., placenta	Can become any type of tissue in the body excluding a placenta	Produce only cells of closely related family of cells	Can produce only one cell type
e.g., 8-16 day old cell embryo	Inner cell mass, iPSC	Mesenchymal stem cells, hematopoietic stem cells	Muscle stem cells, spermatogonial stem cells (SSC)

**Table 2:** Comparison of totipotent, pluripotent, multipotent, and unipotent stem cells [27].

Limbal stem cells are generally considered unipotent adult stem cells. Limbal stem cells (LSCs) are found in the limbus, the junction between the cornea and conjunctiva, and are essential for regenerating the corneal epithelium, which is the outer layer of the cornea that maintains vision. Damage to LSCs, known as limbal stem cell deficiency (LSCD), leads to severe visual impairment due to the loss of new corneal cells [34].

Embryonic stem cells (ESCs) are derived from embryos, as their name suggests, that develop from eggs that have been fertilized in vitro donated for research purposes with informed consent of the donors. Embryonic stem cells are never derived from eggs fertilized inside of a woman's body. Around 3–5 days after a sperm fertilizes an egg, the embryo takes the form of a blastocyst or ball of cells. Embryonic stem cells come from a blastocyst that is 4–7 days old. The embryo (blastocyst), contains an outer cell mass that become part of placenta and an inner cell mass that is capable of generating all the specialized tissues that develop into the human body. Embryonic stem cells come from the inner cell mass of 4-to-7-day old embryo. Embryonic stem cells are obtained by harvesting living embryos which are generally 4-7 days old. The removal of embryonic stem cells invariably results in the destruction of embryo. Embryonic germ cells are obtained from either miscarriages or aborted fetuses. This is known as pluripotent stem cells have the potential to become any cell type and are only found during the first stages of development. These stem cells are grown in vitro such as nerve, skin, intestine, liver, etc for transplantation [35,36].

Embryonic stem cells are capable of undergoing an unlimited number of symmetrical divisions without differentiating (long-term self-renewal). They exhibit and maintain a stable, full (diploid), normal complement of chromosomes (karyotype). Limitless cell renewal capacity can give rise to every cell in the

body induced to form specialized cells of all three germ cell layers (neuron, cardiac muscle, liver cells, pancreatic islets cells). Embryonic stem cells can be grown indefinitely in the laboratory in an unspecialized state retain ability to specialize into many different tissue types, known as pluripotent. They can restore function in animal models following transplantation. Embryonic stem cells are pluripotent, can give rise to differentiated cell types that are derived from all three primary germ layers of embryo endoderm, mesoderm, ectoderm. [35,36].

Embryonic stem cells are most undifferentiated and pluripotent derived from the inner cell mass of a blastocyst, an early-stage embryo that can differentiate into any specialized cell type in the human body. The embryos from which human embryonic stem cells are derived are typically 4 or 5 days old and are a hollow microscopic ball of cells called the blastocyst. Human embryonic stem cells measure approximately 14 $\mu$ m. A significant risk is the potential for embryonic stem cells to form tumors (teratomas) after transplantation, which presents a barrier to their clinical use [35,36].

They possess the unique ability of indefinite self-renewal and hold great potential for regenerative medicine and understanding developmental biology. However, their use raises significant ethical concerns, primarily the destruction of the embryo, and practical challenges exist regarding their safe clinical application. Embryonic stem cells have several advantages. They appear to have the potential to make any cell (flexible). one embryonic stem cell line can potentially provide an endless supply of cells with defined characteristics (immortal), and availability of embryos from in vitro fertilization clinics. Embryonic stem cells also have several disadvantages. They are difficult to differentiate uniformly and homogeneously into a target tissue, immunogenic- embryonic stem cells from a random embryo donor are likely to be rejected after transplantation, capable of forming tumors or promoting tumor formation (tumorigenic), and destruction of developing human life [35,36 ].

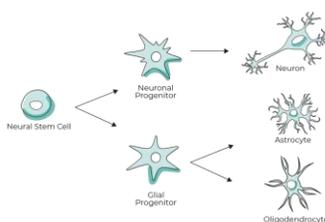
### **Adult stem cells (somatic stem cells)**

Adult stem cells, also known as somatic stem cells are unspecialized and undifferentiated cells found in small numbers among specialized or differentiated cells in a tissue or organ after birth in most adult tissues found throughout the body that can self-renew and differentiate into a limited range of specialized cell types within their original tissue where they are located. In many tissues, they remain inactive or dormant until triggered by injury, disease, or other factors. They are crucial for replenishing dying cells and repairing damaged tissues. Unlike embryonic stem cells, adult stem cells are found in postnatal individuals in tissues like bone marrow, adipose tissue (fat), skin, liver, dental pulp, brain, placenta, umbilical cord, and menstrual blood, among others. These cells can be collected and used in regenerative medicine to differentiate into specialized cells, replacing damaged tissue and promoting repair [37,38].

Adult stem cells are multipotent in nature and give rise to a closely related family of cells within the tissue, e.g., hematopoietic stem cell, which form all the various cells in the blood. Found in developed tissues, these stem cells are multipotent, meaning they can differentiate into a limited range of cell types to repair specific tissues [37,38].

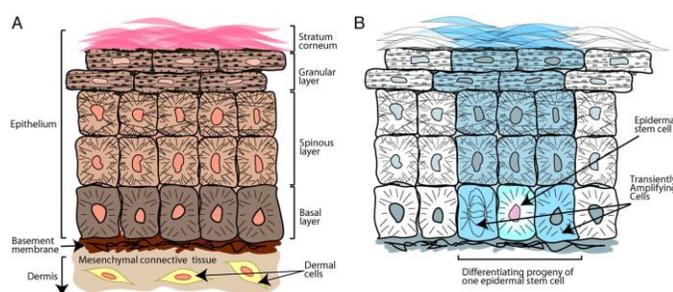
Adult stem cells possess plasticity and trans-differentiation ability to differentiate into multiple cell types. Hematopoietic stem cells (HSCs) are multipotent, have self-renewal capacity and the ability to regenerate

all the different types of blood forming cells [39]. Mesenchymal stem cells (MSCs) are multipotent, exhibit the potential for differentiation into a variety of different cells/tissue lineages, and give rise to osteocytes, chondrocytes, adipocytes, and other connective tissues. MSCs are used to create and repair new body tissues, such as bone, cartilage, and fat cells [40]. Neural stem cells (NSCs) are undifferentiated, self-renewing, multi-potent stem cells in central nervous system give rise to its three major cell types: nerve cells (neurons) and two categories of non-neuronal cells, astrocytes and oligodendrocytes. Neural stem cells (NSCs) have the potential to give rise to offspring cells that grow and differentiate into cells. Neural stem cells can help to treat things such as stroke, spinal cord injury, and Parkinson's disease (Figure 5) [41].



**Figure 5:** Differentiation of neural stem cells [41].

Epithelial stem cells (EPSCs) are multipotent, and responsible for regeneration of the different layers of the epidermis, every day. Many epithelial tissues are capable of regeneration, that is, they are capable of rapidly replacing damaged and dead cells. Stem cells in the skin can self-renew and differentiate into different cell lineages of the skin and are multipotent in nature. Only the basal layer, next to the dermis, cells that divide are present (Figure 6). Hair follicle stem cells ensure constant renewal of the hair follicles. The stem cells at the base of the skin stop proliferating and start differentiating into the cells that form the skin itself [42,43].



**Figure 6:** Stem cells in the skin epithelium: (A) Skin epithelial histology (B) Diagram of the epidermal proliferative unit [43].

Sources of adult stem cells include various tissues in the body. Bone marrow is a rich source of hematopoietic (blood-forming) and mesenchymal stem cells. Adipose tissue providing adipose derived stem cells. Blood contains hematopoietic stem cells, which can be harvested through a process similar to blood donation. Adult stem cells are also found in other tissues such as the epidermis, retina, brain, liver, heart, skeletal muscle, gut, skin, and dental pulp. Adult type stem cells can be derived from various pregnancy related tissue such as umbilical cords, placentas and amniotic fluid. Neural stem cells have been removed from specific areas in post-mortem human brains from cadavers as late as 20 hours following

death [37,38,44].

Advantages of using adult stem cells are that the patient's own cells could be expanded in culture and then reintroduced into the patient. The use of the patient's own adult stem cells would mean that there will be no immune rejection. Some adult stem cells are easy to harvest (skin, muscle, bone marrow, and fat) and relative ease of procurement, though somewhat specialized, inducement may be simpler, non-tumorigenic, and no harm to the donor. Adult stem cells are preferable to embryonic stem cells because adult stem cells exist naturally in our body, and provide a natural repair mechanism for many tissues. They belong in the microenvironment of an adult body, while embryonic stem cells belong in the microenvironment of the early embryo, where they tend to cause tumors and immune system reactions (Table 3) [45].

**Disadvantages of adult stem cells:** They are limited in quantity, can sometimes be difficult to obtain in large numbers; Finite - may not live as long as embryonic stem cells in culture, and less flexible - may be more difficult to reprogram to form other tissue types [45].

Embryonic stem cells	Adult stem cells
Cell lines last and last and last	Cell lines do not last
Multipotent	Not multipotent
Easy to find	Hard to locate
Ethical issues- when does life begin?	No ethical issues

**Table 3:** Comparison of embryonic versus adult stem cells [45].

### Umbilical cord stem cells

Umbilical cord stem cells are stem cells found in the blood of the umbilical cord and placenta after a baby's birth, and they can be stored for future use in treating life-threatening diseases. These potent, undifferentiated cells are valuable because of their ability to self-renew and differentiate into specialized cell types, such as blood, bone, and neural cells. The primary clinical application of cord blood stem cells is in transplants to rebuild the hematopoietic and immune systems for conditions like leukemia, lymphoma, and various immunodeficiencies. Umbilical cord stem cells are unspecialized cells that can divide indefinitely and differentiate into various specialized cells in the body, such as skin, muscle, or nerve cells. Hematopoietic stem cells found in cord blood are responsible for forming the blood and immune systems and are the primary focus of cord blood stem cell transplants. Mesenchymal stem cells from the cord tissue may also have the potential to develop into other types of cells, like bone, neural, and endothelial (blood vessel) cells [46-48].

Umbilical cord stem cells are collected from the blood remaining in the umbilical cord and placenta immediately after a baby's birth, a process that is risk-free and painless for the mother and newborn. Families can choose to store their baby's cord blood for private use or donate it to a public cord blood bank to help patients in need. The collected cord blood is processed to isolate the stem cells and then cryopreserved (frozen) in specialized cord blood banks. When a patient needs a transplant, a matched cord blood unit can be thawed and transplanted to restore their healthy blood-forming system

[46-48].

Umbilical cord stem cells are technically considered a type of adult stem cell, although they are sometimes referred to as "tissue stem cells" to distinguish them from embryonic stem cells. Unlike embryonic stem cells, which come from embryos, umbilical cord stem cells are collected after birth from the umbilical cord blood or tissue and are not involved in the controversial destruction of embryos. The importance of cord blood stem cells is that they have been used to treat 70 different diseases, including leukemia, lymphoma, and inherited diseases of RBCs, immune system, and metabolic disorders [46-48].

Umbilical cord stem cells are very valuable in disease treatment. Cord blood transplants are a proven method to treat a wide range of conditions, including certain types of leukemia, lymphoma, sickle cell disease, aplastic anemia, and some immune system disorders. Compared to bone marrow transplants, cord blood transplants offer several benefits, such as being a readily available "off-the-shelf" product for urgent use, less stringent matching requirements, and a lower incidence of chronic graft-versus-host disease. Beyond established treatments, cord blood stem cells hold promise for future cell and tissue therapies due to their multipotential nature [48,49].

### **Somatic cell nuclear transfer (therapeutic cloning)**

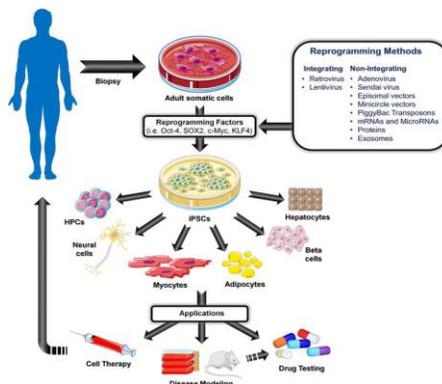
Scientists first remove the nucleus from a normal egg cell of a woman. They, then extract a nucleus from a somatic cell (that is, any body's cell other than an egg or sperm) from a patient who needs an infusion of stem cells to treat a disease or injury, and insert the nucleus into the egg. The egg, which now contains the patient's genetic material, is allowed to divide and soon forms a hollow sphere of cells called a blastocyst. The cells from the inner cell mass are isolated and used to develop new embryonic stem cell (ESC) lines [50,51].

### **Induced pluripotent stem cells (ipscs)**

Pluripotent stem cells (PSCs) form cells of all germ layers but not extraembryonic structures, like placenta, e.g., embryonic stem cells (ESCs) derived from the inner cell mass of preimplantation embryos, and induced pluripotent stem cells (iPSCs) are a type of pluripotent stem cell derived from adult somatic cells that have been genetically reprogrammed to an embryonic stem (ES) cell like state. Their culturing and utilization are very promising for present and future regenerative medicine. Induced pluripotent stem cells (iPSCs) are artificially created stem cells, derived from a patient's own (autogenic, patient-specific) adult cells (like skin or blood) and reprogramming adult cells to an embryonic-like state. They can be grown indefinitely in culture in an undifferentiated state. Like embryonic stem cells, iPSCs are pluripotent, meaning they can develop into any cell type in the body. This breakthrough technology, pioneered by the Yamanaka lab in 2006 and 2007, avoids the ethical controversies surrounding embryonic stem cells. iPSCs have wide-ranging applications in research, including disease modeling and drug screening, and hold promise for personalized cell therapies and regenerative medicine [52-54].

Induced pluripotent stem cells (iPSCs) can be created by reprogramming adult somatic (non-stem) cells, such as like fibroblasts from skin or blood cells, are genetically modified to express specific "reprogramming factors" to an embryonic stem cell-like state, achieved by introducing specific transcription factors into the cells that initiate the change. The original breakthrough involved the

introduction of four key genes Oct4, Sox2, Klf4, and c-Myc, known as reprogramming factors or Yamanaka factors. These genes are critical for reversing the differentiated state of the somatic cell and restoring its pluripotency. The expression of these factors "de-differentiates" the cells to pluripotent, forcing them to acquire the characteristics of embryonic stem cells. Induced pluripotent stem cells (iPSCs) are generated by reprogramming adult somatic cells, such as skin or blood cells, back into an embryonic-like pluripotent state through the forced expression of key transcription factors. The original method used four factors Oct4, Sox2, Klf4, and c-Myc delivered via retroviruses. While effective, this method can lead to vector integration into the host genome, raising concerns about potential tumors. Subsequent research has explored methods using non-integrating vectors, small molecules, and direct delivery of proteins to improve safety and efficiency for clinical applications. To address safety concerns, researchers developed alternatives to viral vectors, known as non-integrating methods such as episomal vectors, minicircle DNAs, plasmids, mRNAs, recombinant proteins, and small molecules. Certain small molecules can either replace some of the reprogramming factors or enhance the reprogramming efficiency when used alongside the factors (Figure 7) [55-58].



**Figure 7:** Production and applications of induced pluripotent stem cells [58].

After reprogramming, the cells become induced pluripotent stem cells and acquire the characteristics of embryonic stem cells such as unlimited capacity for self-renewal with the capacity to proliferate indefinitely in a laboratory setting. With the ability to differentiate into any cell type in the body (pluripotency), iPSCs can differentiate into cells from any of the three germ layers (ectoderm, mesoderm, and endoderm), forming any tissue type. Possess similar gene expression profiles and chromatin methylation patterns to embryonic stem cells. Because they are derived from a patient's own cells, iPSCs are genetically matched to the individual (patient-specific) eliminating the risk of immune rejection in future cell therapies [55-58].

### Applications Of Induced Pluripotent Stem Cells

The significance of the development of iPSC technology was a major breakthrough, providing a source of pluripotent cells without the need for human embryos. It has significantly advanced the basic research and clinical applications, opening new avenues for understanding human development and treating various diseases [56,57].

- **Disease modeling:** iPSCs from patients with genetic diseases can be used to create in vitro models

of the disease, helping researchers understand its underlying mechanisms and the development of symptoms [56].

- **Drug screening:** These disease models allow for the high-throughput screening of potential new drugs [57].
- **Cell therapy and regenerative medicine:** iPSCs can be differentiated into specific cell types (like neurons or heart cells) to replace damaged or defective cells in a patient. Placental stem cells, like umbilical cord blood and bone marrow stem cells can be used to cure chronic blood-related disorders such as sickle cell disease, thalassemia, and leukemia. Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system [56-60].
- **Toxicological studies:** The ability to generate various cell types from iPSCs can also be used to study the potential toxic effects of substances [57].

### Sources of stem cells

Stem cells may be derived from autologous, allogeneic or xenogeneic sources. Histocompatibility is prerequisite for transplantation of allogeneic stem cells. Fetal tissue is the best current tissue source for human neural stem cells; however ethical issues are a major concern. Potential sources of stem cells include fetal tissue that becomes available after an abortion, placental tissue, excess embryos from assisted reproductive technologies such as commonly used in fertility clinics, embryos created through in vitro fertilization specifically for research purpose, from umbilical cord blood, and bone marrow. In addition, neural stem cells, hematopoietic stem cells and mesenchymal stem cells can be harvested From Fetal Blood and Fetal Tissue [59,60].

### Conclusion

Stem cell technology has significantly advanced the field of regenerative medicine, offering promising strategies for the restoration and functional repair of damaged tissues and organs. As discussed in this review, various stem cell types, including embryonic stem cells, adult stem cells, and induced pluripotent stem cells, possess unique biological properties that make them valuable for therapeutic applications. Progress in stem cell isolation, differentiation, tissue engineering, and gene-editing technologies has expanded the scope of regenerative therapies and accelerated their transition toward clinical use.

Despite these advances, several challenges remain, including ethical concerns, immune rejection, tumorigenic potential, scalability, and stringent regulatory requirements. Addressing these limitations through improved safety profiling, standardized protocols, and interdisciplinary collaboration will be essential for successful clinical translation. Continued research and carefully designed clinical trials are expected to further refine stem cell-based therapies and improve their efficacy and safety. Overall, stem cell technology holds immense potential to reshape regenerative medicine, offering innovative solutions for previously incurable diseases and paving the way toward personalized and regenerative healthcare.

### Availability of data and materials

Since this is a review article, the issue of raw data may not arise. However, raw data will be available on

request.

### Competing interest

The author declares that they have no competing interest.

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### Author's contribution

The author was solely responsible for study design, literature review, data collection, data analysis and manuscript writing.

### References

1. Kolios G, Moodley Y. (2013) Introduction to stem cells and regenerative medicine. *Respiration*. 85(1):3-10.
2. Tandon V, Kondapurkar US, Chowda HK, Kumar A. (2024) Regenerative medicine and stem cell therapy: an evolving paradigm in modern healthcare. *Europ J Cardiovasc Med*. 14(2):270-278.
3. Poliwoda S, Noor N, Downs E, Schaaf A, Cantwell A, et al. (2022) Stem cells: a comprehensive review of origins and emerging clinical roles in medical practice. *Orthop Rev (Pavia)*. 14(3):37498.
4. Della Rocca Y, Mazzone A, Marconi GD, Trubiani O, Pizzicannella J, et al. (2025) Stem cells in regenerative medicine: a journey from adult stem cells to induced pluripotent cells. *Int. J. Mol. Sci*. 26:8255.
5. Olson JL, Atala A, Yoo JJ. (2011) Tissue engineering: current strategies and future directions. *Chonnam Med J*. 47(1):1-13.
6. Fontes PA, Thomson AW. (1999) Stem cell technology. Interview by Abi Berger. *BMJ*. 319(7220):1308.
7. Biehl JK, Russell B. (2009) Introduction to stem cell therapy. *J Cardiovasc Nurs*. 24(2):98-103
8. Hoang DM, Pham PT, Bach TQ. (2022) Stem cell-based therapy for human diseases. *Sig Transduct Target Ther*. 7:272.
9. Schuldiner M, Yanuka O, Itskovitz-Eldor J, Melton DA, Benvenisty N. (2009) Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. *Proc Natl Acad Sci*. 97(21):11307-11312.
10. Lott K, Collier P, Ringor M, Howard KM, Kingsley K. (2023) Administration of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) to induce neural differentiation of dental pulp stem cells (DPSC) isolates. *Biomedicines*. 11:255.
11. Goldman JM, Horowitz MM. (2002) The international bone marrow transplant registry. *Int J Hematol*. 76(1):393-7.
12. Gupta DR, Singh S. (2024) Stem cells: Current applications and future prospects. *Indian J Med Sci*. 76:2-6.
13. Sangmin Lee, Hwa In Yoon, Jin Hee Na, SangminJeon, Seungho Lim, et al. (2017) In vivo stem cell tracking with imageable nanoparticles that bind bioorthogonal chemical receptors on the stem cell surface. *Biomaterials*. 139:12-29.
14. Morrison SJ, Spradling AC. (2008) Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. *Cell*. 132(4):598-611.
15. Jing Zhao, Ana Angelova Volponi, Ana Caetano, Paul T. (2020) Sharpe. *Mesenchymal Stem Cells in Teeth*, Editor(s): MoneZaidi. *Encyclopedia of Bone Biology*. Academic Press. 2020:109-118.
16. Sundelacruz S, Kaplan DL. (2009) Stem cell- and scaffold-based tissue engineering approaches to osteochondral regenerative medicine. *Semin Cell Dev Biol*. 20(6):646-55.
17. Nicholas D. Evans, Eileen Gentleman, Julia M. Polak. (2006) Scaffolds for stem cells. *Materials Today*. 9(12):26-33.

18. Valenti MT, Serena M, Carbonare LD, Zipeto D. (2019) CRISPR/Cas system: An emerging technology in stem cell research. *World J Stem Cells*. 11(11):937-956.
19. Veronica E Farag, Elsie A Devey, Kam W Leong. (2025) The interface of gene editing with regenerative medicine. *Engineering*. 46:73-100.
20. Camia B, Monti M. (2025) From biological waste to therapeutic resources: a comprehensive review of stem cell sources, characterization, and biomedical potentials. *Stem Cell Rev and Rep*. 22:5–25.
21. Dhakad GG, Fate BO, Pandav AR, Shrirao AV, Kochar NI, et al. (2023) Review on stem cell therapy and its various aspects. *Res J Pharmacol Pharmacody*. 15(2):77-6.
22. Marwan T, M Abofila, Azab E, Azab Amal MA. Al Shebani, et al. (2021) Stem cells: insights into niche, classification, identification, characterization, mechanisms of regeneration by using stem cells, and applications in joint disease remedy. *J Biotech and Bioprocessing*. 2(1).
23. Nicolas H Zech. (2004) Adult stem cell manipulation and possible clinical perspectives. *J Repro Med Endocrinol*. 1(2):91-99.
24. Kalika Prasad, Dasaradhi Palakodeti. (2024) Cellular and molecular mechanisms of development and regeneration. *Development*. 151(11):dev203023.
25. Das D, Fletcher RB, Ngai J. (2020) Cellular mechanisms of epithelial stem cell self-renewal and differentiation during homeostasis and repair. *Wiley Interdiscip Rev Dev Biol*. 9(1):e361.
26. Chen YG, Ezhkova E, Ostankovitch M. (2016) Molecular mechanisms regulating stem cells fate. *J Mol Biol*. 428(7):1407-8.
27. Singh VK, Saini A, Kalsan M, Kumar N, Chandra R. (2016) Describing the stem cell potency: the various methods of functional assessment *and in silico* diagnostics. *Front Cell Dev Biol*. 4:134.
28. Maria Betdasco, Manel Esteller. (2011) DNA methylation in stem cell renewal and multipotency. *Stem Cell Res Thera*. 2(5):42.
29. Cai J, Chen H, Xie S, Hu Z, Bai Y. (2022) Research progress of totipotent stem cells. *Stem Cells Dev*. 31(13-14):335-345.
30. Romito A, Cobellis G. (2016) Pluripotent Stem cells: current understanding and future directions. *Stem Cells Int*. 2016:9451492.
31. Hala M Gabr, Wael Abo El-Kheir. (2023) Chapter 3 - Stem cells: definition, biological types, classifications, and properties. Editor(s): Hala M. Gabr, Wael Abo El-Kheir. *Stem Cell Therapy*. Academic Press. 21-33.
32. Ravichandran VijayaAbinaya, Pragasam Viswanathan. (2021) Chapter 2 - Biotechnology-based therapeutics. Editor(s): Yasha Hasija. *Translational Biotechnology*. Academic Press. 27-52.
33. Sobhani A, Khanlarkhani N, Baazm M, Mohammadzadeh F, Najafi A, et al. (2017) Multipotent Stem Cell and Current Application. *Acta Med Iran*. 55(1):6-23.
34. Gonzalez G, Sasamoto Y, Ksander BR, Frank MH, Frank NY. (2018) Limbal stem cells: identity, developmental origin, and therapeutic potential. *Wiley Interdiscip Rev Dev Biol*. 7(2):10.1002/wdev.303.
35. Duncan E Crombie, Martin F Pera, Martin B Delatycki, Alice Pébay. (2016) Using human pluripotent stem cells to study Friedreich ataxia cardiomyopathy. *Inte J Cardiol*. 212:37-43.
36. Ilic D, Ogilvie C. (2017) Concise review: human embryonic stem cells—what have we done? what are we doing? Where are we going? *Stem Cells*. 35:17-25.
37. Cable J, Fuchs E, Weissman I, Jasper H, Glass D, et al. (2020) Adult stem cells and regenerative medicine—a symposium report. *Ann N Y Acad Sci*. 1462(1):27-36.
38. Montagnani Stefania, Rueger Maria A, Hosoda Toru, Nurzynska Daria. (2016) Adult stem cells in tissue maintenance and regeneration, *Stem Cells International*. 7362879:2.
39. Lee JY, Hong SH. (2020) Hematopoietic stem cells and their roles in tissue regeneration. *Int J Stem Cells*. 13(1):1-12.
40. Uccelli A, Moretta L, Pistoia V. (2008) Mesenchymal stem cells in health and disease. *Nat Rev Immunol*.

- 8:726-36.
41. Tang Y, Yu P, Cheng L. (2017) Current progress in the derivation and therapeutic application of neural stem cells. *Cell Death Dis.* 8:e3108.
  42. Blanpain C, Horsley V, Fuchs E. (2007) Epithelial stem cells: turning over new leaves. *Cell.* 128(3):445-58.
  43. L Alonso, E. Fuchs. (2003) Stem cells of the skin epithelium. *Proc Natl Acad Sci. USA.* 100 (1):11830-35.
  44. Poliwoda S, Noor N, Downs E, Schaaf A, Cantwell A, et al. (2022) Stem cells: a comprehensive review of origins and emerging clinical roles in medical practice. *Orthop Rev (Pavia).* 14(3):37498.
  45. Leventhal A, Chen G, Negro A, Boehm M. (2012) The benefits and risks of stem cell technology. *Oral Dis.* 18(3):217-22.
  46. Weiss ML, Troyer DL. (2006) Stem cells in the umbilical cord. *Stem Cell Rev.* 2(2):155-62.
  47. Obeagu EI. (2025) Umbilical cord blood: a comprehensive review of protective and restorative properties in clinical applications - a narrative review. *Ann Med Surg (Lond).* 87(10):6618-25.
  48. David McKenna, Jayesh Sheth. (2011) Umbilical cord blood: Current status & promise for the future. *Indian J Med Res.* 134(3):261-269.
  49. Pauline Damien, David SA. (2015) Regenerative therapy and immune modulation using umbilical cord blood-derived cells. *Biology of Blood and Marrow Transplantation.* 21:1545-54.
  50. Tian XC, Kubota C, Enright B, Yang X. (2003) Cloning animals by somatic cell nuclear transfer--biological factors. *Reprod Biol Endocrinol.* 1:98.
  51. Li y, Sun S, Xu Y. (2025) Efficient somatic cell nuclear transfer by overcoming both pre- and post-implantation epigenetic barriers. *Adv Sci.* 12:(37):12, e04669.
  52. Ye L, Swingen C, Zhang J. (2013) Induced pluripotent stem cells and their potential for basic and clinical sciences. *Curr Cardiol Rev.* 9(1):63-72.
  53. Cerneckis J, Cai H, Shi Y. (2024) Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Sig Transduct Target Ther.* 9:112
  54. Shinya Yamanaka. (2012) Induced pluripotent stem cells: past, present, and future. *Cell Stem Cell.* 10(6):678-684.
  55. Zhao C, Ikeya M. (2018) Generation and Applications of Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells. *Stem Cells Int.* 2018:9601623.
  56. Salem NA. (2019) Biomedical Applications of Induced Pluripotent Stem Cells. *Annals Stem Cell Regenerat Med.* 2(1):1013.
  57. Shu Nakao, Dai Ihara, Koji Hasegawa, Teruhisa Kawamura. (2020) Applications for induced pluripotent stem cells in disease modeling and drug development for heart diseases. *European Caadiology Review.* 15:e02.
  58. Naoshi Sugimoto, Koji Eto. (2021) Generation and manipulation of human iPSC-derived platelets. *Cell Mole Life Sci.* 78(4):1-17.
  59. Singh A, Khanna M, Gulati A, Sinha G, Verma S. (2022) Sources of mesenchymal stem cells and its potential. *IP Inte J Orthop Rheumatol.* 8(1):4-8.
  60. Poliwoda S, Noor N, Downs E, Schaaf A, Cantwell A, et al. (2022) Stem cells: a comprehensive review of origins and emerging clinical roles in medical practice. *Orthop Rev (Pavia).* 14(3):37498.