

The Potential of Stem Cells in Regenerative Medicine, Diseases Therapeutics and Research

Tamirat Salile Sada

Institute of Biotechnology, Addis Ababa University, Addis Ababa, Ethiopia

Email address:

tamewoldia@gmail.com

To cite this article:

Tamirat Salile Sada. The Potential of Stem Cells in Regenerative Medicine, Diseases Therapeutics and Research. *International Journal of Microbiology and Biotechnology*. Vol. 10, No. 1, 2022, pp. 1-15. doi: 10.11648/j.cb.20221001.11

Received: February 10, 2022; **Accepted:** March 17, 2022; **Published:** April 8, 2022

Abstract: Stem cells are a form of indistinct cells with the capability to self-renew and replicate. Stem cells originate from a single cell and differentiate into a range of cells and organs in the normal course of things. Stem cells can be used to heal damaged cells or rebuild tissues in cellular treatment. Furthermore, stem cells have advanced our knowledge of both development and disease pathogenesis. Cell lines that are particular to a disease can be produced and employed in medication research. Despite considerable advancements in stem cell biology, ethical concerns about embryonic stem cells, tumor development, and rejection limit their application. Many of these constraints, however, are being circumvented, which could lead to considerable breakthroughs in disease management. This session covers the basics of stem cells, such as their definition, origin, and classification, as well as their applications in regenerative therapy and cell therapy. Stem cells are classified as pluripotent, multipotent, totipotent, or unipotent depending on their potential, and as embryonic stem cells, adult stem cells, or induced pluripotent stem cells based on their origin. The goal of embryonic stem cells, adult stem cells, and induced pluripotent stem cells in regenerative therapy, a relatively new field of medicine, is to restore the function of specific tissue and/or organs in patients who have suffered catastrophic injuries or chronic disease conditions. The clinical relevance of stem cells in treating cancer, vision loss, diabetes, and burns has sparked a surge in scientific and medical interest in stem cells. In addition, stem cells will be explored for disease modeling and medication development, as well as stem cell and tissue banks for various research goals and future usage. In addition, the limitations of stem cell-based treatments will be investigated.

Keywords: Cell Therapy, Regenerative Therapy, Stem Cells, Therapeutics

1. Introduction

As a regenerative medicine and therapies modality, stem cell-based therapy is regarded as one of modern science's and medicine's most promising fields. Such advanced technology opens the door to a slew of novel and potentially curative treatments for some of humanity's deadliest ailments. Appropriate, safe, and functional stem cells or stem cell-derived cells/organoids must be created employing an efficient, but simple, and rapid differentiation procedure for their practical application in disease modeling, regeneration, and cell therapy [12].

Stem cell-based therapy refers to any treatment for a disease or medical condition that entails the use of any type of viable human stem cells, including ESCs, iPSCs, and adult stem cells for autologous and allogeneic therapies.

Preclinical and clinical evidence of stem cell-based

therapeutic effects suggests that regenerative approaches could one day be used to treat a wide range of diseases [1, 58]. This Special Issue describes and examines the current state of stem cell therapies, including ESCs, ASCs, and iPSCs. Stem cells were first used in bone marrow transplants (BMTs) in the 1960s, a surgery that was originally used to treat cancer and genetic blood disorders. Around 60,000 BMT operations use stem cells each year all across the world. Stem cells from peripheral and umbilical cord blood are increasingly being employed in this procedure instead of bone marrow. In addition to their utility in BMTs, stem cells are being researched for their ability to replenish or even mend damaged tissues and cells in the body.

In order to better understand cell differentiation signals and mechanisms, stem cells are increasingly being used as research tools. This is beneficial not only in determining the source of illness, but also in generating new remedies. Because stem

cells have the ability to produce large numbers of specialized cells, they are increasingly being utilized to assess the safety of new medications without the use of animals [11].

Cancer stem cells, for example, are used to test potential anti-tumor drugs. Stem cells are being explored in the field of regenerative medicine for their ability to replace cells lost in degenerative illnesses and to repair cells in damaged tissues. There are treatments for retinal diseases, neurological ailments such as Parkinson's and Alzheimer's disease, heart disease such as post-ischemic stroke, and type 1 diabetes.

Work on stem cells and organ regeneration in modern medicine dates back to the 1950s, when the first efforts at bone marrow transplantation in animals were made. This groundbreaking study paved the door for human bone marrow transplantation, which is currently widely used to treat a variety of blood diseases.

This novel therapeutic approach demonstrates that stem cells hold considerable promise as a cell source for regenerative medicine and cell therapy, and has piqued the curiosity of basic scientists, physicians, and the general public.

These stem cells are being produced for a surprising Adult stem cells can be utilized to replace a patient's own cells In case of iPSCs components of immunorejection, ethical, and tumorigenesis are all uncontroversial. As a result, they have a particular benefit in that they are accepted by all patients and are widely utilized in clinical trials [44].

ESCs and iPSCs are progressively being verified for their therapeutic effects and safe use in the treatment of a variety of disorders, including neurological diseases, cancer, eye disease, wounds, and burns [8].

In addition to being effective in the treatment of disease, stem cells can also be used to learn more about it. Recent

advancements in the field of iPSCs, in particular, have paved the way for a new generation of disease modeling [35]. iPSCs can be generated from a variety of affected populations, expanded, and differentiated into disease-related cell types (e.g., neurons and cardiomyocytes) that can be cultured as two-dimensional monolayers or included in stem cell-derived organoids, and then used to improve disease mechanisms and test therapeutic interventions.

2. Stem Cell Technology and Its Classification

2.1. Overview of Stem Cell Technology

Stem cells are unspecialized cells that give rise to differentiated cells, which are the fundamental units of tissue and organs. They are ancestor cells to one or more specialized cells and can be found in the embryonic, fetal, and adult stages of life. In the post-natal and adult periods of life, tissue-specific stem cells are located in differentiated organs and play a vital role in organ regeneration following injury [15]. The three primary qualities of stem cells are self-renewal (the ability to proliferate widely), clonality (the ability to emerge from a single cell), and potency (the ability to differentiate into multiple cell types). Both external and internal signals, such as physical contact between cells, can influence stem cell specialization. External signals, such as physical contact between cells or chemical secretion by surrounding tissue, and internal signals, which are controlled by genes in DNA, impact the stem cell specialization process.

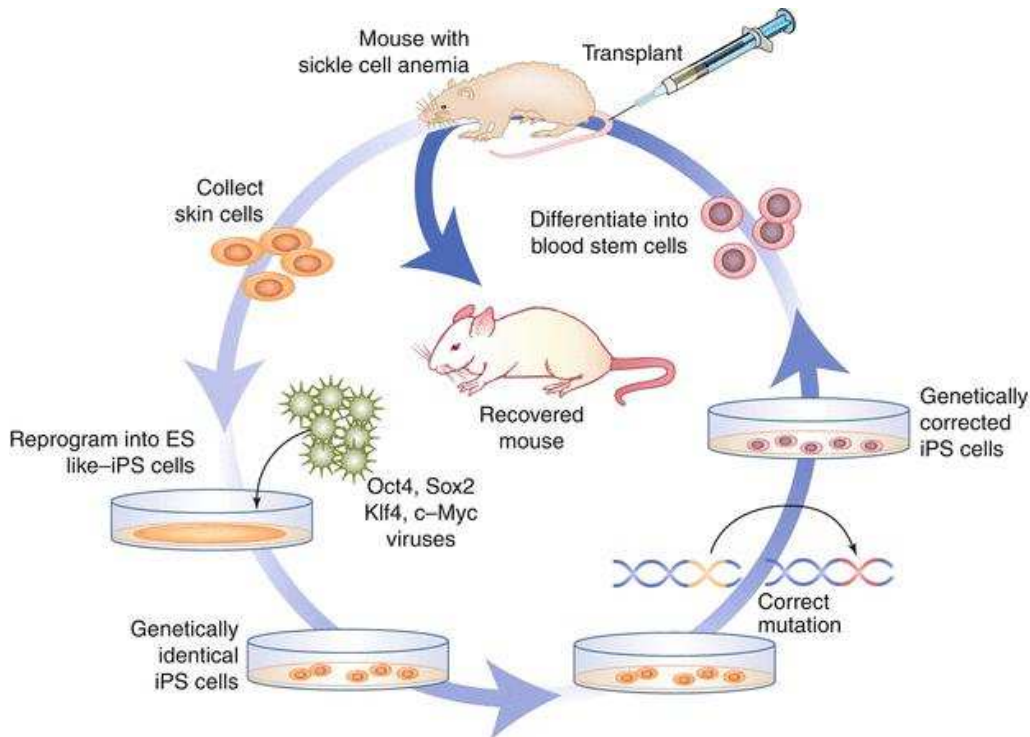


Figure 1. In an animal model, a method for producing iPS cells and curing sickle cell anemia [23].

Stem cells also serve as the body's internal repair system. As long as an organism is alive, it can replenish and generate new cells indefinitely. Stem cell activity varies depending on the organ; for example, in bone marrow, division is continual, whereas in organs like the pancreas, division occurs only under certain physiological conditions [30].

From the earliest stages of development (embryonic stem cells (ESCs) and fetal stem cells) until adulthood (different adult stem cells), stem cells can be found in the human body [5].

Diverse types of stem cells have different capacities for proliferation and differentiation, as well as different cell sources, which can lead to a wide range of applications in regenerative medicine, cell therapy, and disease modeling.

Adult stem cells, embryonic stem cells (ESCs), as well as induced pluripotent stem cells (iPSCs) are all commonly employed in fundamental science and therapeutic research [14].

Embryonic stem cells (ESCs) are formed from the blastocyst and have a higher capacity for self-renewal and potency, but stem cells found in adult tissue have limited self-renewal since they can only develop into tissue-specific cells and no longer multiply. Adult stem cells are undifferentiated and can be detected in the body's differentiated cells following development. These cells' job is to allow for the healing, growth, and replacement of cells that are lost every day. The differentiation possibilities available to these cells are limited.

Artificial pluripotent stem cells, or iPSCs, are stem cells that can be reprogrammed from a variety of somatic cells, such as skin and blood cells that is then used for treatment of different disease like anemia as indicated in (figure 1). In vitro, iPSCs have the same ability to proliferate and differentiate as ESCs [32].

2.2. Stem Cell Classification

2.2.1. Categorization Based on Potency

The ability of stem cells to differentiate into different cell types can be utilized to classify them. The five basic classes are totipotent, pluripotent, multipotent, oligopotent, and unipotent [18, 30].

(i). Totipotent

Totipotent stem cells can divide and develop into every form of cell in the human body. Totipotency allows cells to

form both embryonic and extraembryonic structures while also allowing for maximum differentiation. A zygote, which is generated when a sperm fertilizes an egg, is an example of a totipotent cell. These cells can develop into any of the three germ layers or a placenta later on. The blastocyst's inner cell mass becomes pluripotent after around 4 days. Pluripotent cells come from this structure.

(ii). Pluripotent

PSCs can make cells from all three germ layers, but not extraembryonic tissues like the placenta. Embryonic stem cells are one example (ESCs). ESCs are produced from the inner cell mass of preimplantation embryos. Another example is induced pluripotent stem cells (iPSCs) derived from the epiblast layer of implanted embryos. Starting with fully pluripotent cells like ESCs and iPSCs and ending with less potent cells like multi-, oligo-, and unipotent cells, their pluripotency is a gradient.

One method for measuring their activity and spectrum is the teratoma development assay. iPSCs (induced pluripotent stem cells) are stem cells that are produced from somatic cells and behave similarly to adult stem cells. Their cultivation and application hold a lot of promise for today's and tomorrow's regenerative medicine [30].

(iii). Multipotent

PSCs have a wider differentiation range than multipotent stem cells, but they can specialize in certain cell lineages. For example, a hematopoietic stem cell (HSC) can develop into a variety of blood cells. After differentiation, the HSC becomes an oligopotent cell. Its differentiation ability is then restricted to cells of the same lineage. Certain multipotent cells, on the other hand, have the ability to transform into unrelated cell types, signaling that they should be classified as such pluripotent cells [55].

(iv). Oligopotent

Oligopotent stem cells can differentiate into a wide range of cell types. A myeloid stem cell, for instance, can divide into white blood cells but not red blood cells.

(v). Unipotent

Unipotent stem cells have the smallest capacity for differentiation and the unique ability to divide many times. Their final attribute qualifies them as a potential regenerative medicine therapy candidate. Only one type of cell, such as dermatocytes, can be formed by these cells.

Table 1. Stem cell classification, description and examples.

Classification of stem cells based on potency		
Cell type	Description	Examples
Totipotent	Each cell can develop in to a new individual	Cells from early (1-3) days embryo
Pluripotent	Cells can form (over) cell types	Some cells of blastocysts (5-14 days)
Multipotent	Cells differentiated but can form a limited cell type	Fetal tissue, cord blood and adult stem cells
Oligopotent	Ability to differentiate in too few cells	Adult lymphoid or myeloid cell
Unipotent	Ability to produce cells their own type, self-renew	Adult muscle stem cells

2.2.2. Division Based on Their Origin

(i). Embryonic Stem Cells (ESCs)

After 4-5 days after conception, pluripotent, self-renewing cells called embryonic stem cells can be extracted from mouse or human blastocysts [66]. They can be maintained in culture as undifferentiated cell lines and then coaxed to differentiate into any cell line [61]. They can differentiate into endoderm, mesoderm, and ectoderm embryonic germ layers, as well as any form of somatic cell. As a result, tissue regeneration therapy has a lot of promise for them.

(ii). Adult Stem Cells (ASCs)

Adult stem cells are any stem cells derived from mature tissue; they can only create a limited number of cell types and can be found in the tissues of a fully developed child (whole embryo) or adult. Because of the stage of development of these cells, they have limited potential compared to stem cells produced from embryos and fetuses [45]. They are referred to their tissue origin and play an important function in tissue repair and regeneration. Adult

stem cells can be found in abundance in bone marrow.

Pluripotent stem cells that have been induced.

(iii). Induced Pluripotent Stem Cells

(iPSCs) are pluripotent stem cells that are created artificially from a non-pluripotent adult differentiated somatic cell, as indicated in the diagram (Figure 2). To turn an adult somatic cell into an induced pluripotent stem cell (iPSC), the initial step was to compel the expression of specific genes.

It has been reported that forcing the expression of a set of transcription factors can reprogram human and mouse somatic cells into iPSCs. A variety of alternative methods for creating iPSC have been documented, and these will be discussed in the genetic modification part of this study.

Fibroblasts are the most common source of iPSC, but the liver, pancreatic b cells, and mature B cells have also been used [67]. Despite their disparate origins, ESC and iPSC have a lot of characteristics. Their growth patterns, gene expression profiles, and epigenetic profiles.

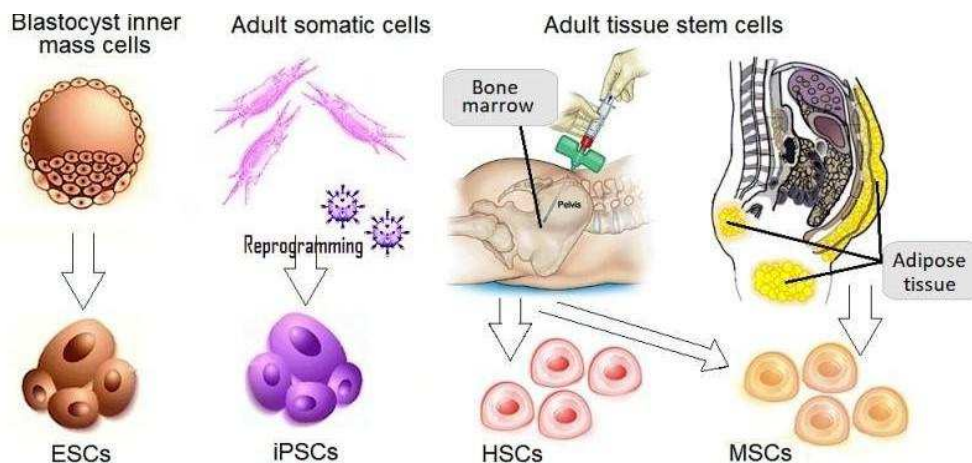


Figure 2. Various types of stem cells and their origins [7].

3. Stem Cells and Regenerative Therapy

Regenerative therapy, the most recent and rapidly growing branch of medical science, is concerned with the functional regeneration of tissues or organs in patients suffering from catastrophic accidents or chronic disease. Donated tissues and organs are now unable to meet the transplantation needs of the elderly and sick, necessitating the search for alternatives. Stem cells have an unlimited potential for cell division and the ability to transdifferentiate into different types of cells, and they have lately emerged as a frontline regenerative medicine source for the repair of tissues and organ abnormalities caused by congenital diseases, disease, and aging.

All of the body's tissue and organ systems are built on stem cells, and they play a variety of roles in disease progression, development, and tissue repair in the host. Based on their regenerative applications, stem cells are

divided into embryonic stem cells, tissue specific progenitor stem cells, mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs), bone marrow stem cells (BMSCs), and induced pluripotent stem cells (iPSCs) [59]. Stem cell transplantation can be autologous, allogenic, or syngeneic for tissue regeneration and immunolysis of pathogen or malignant cells. To avoid the effects of host-versus-graft rejection in tissue and organ transplants, tissue typing of human leucocyte antigens is used, as well as the use of immune suppressants. Tissue engineering methods integrate the principles of cell transplantation, material science, and microengineering to create organoids that can be utilized to restore the physiological function of damaged tissue and organs in current stem cell regenerative medicine approaches. Tissue engineering is a method of growing embryonic tissue on biodegradable 3D scaffolds [16, 22]. The best scaffolds promote cell adhesion and ingrowth, match target tissue dynamics, support angiogenesis and neovascularization for correct tissue perfusion, and are nonimmunogenic to the host,

so they don't require systemic immune suppressants. The amount of stem cells in a tissue transplant influences the regeneration outcome, hence *ex vivo* growth of transplantable stem cells is essential [19, 59].

3.1. Regenerative Therapy with ESCs

There is a lot of interest in using ES cells in basic biology research as well as transplantation therapy since they can differentiate into therapeutically beneficial cell types as dopamine neurons, cardiomyocytes, and B-cells. Both applications require a high level of lineage allocation and growth control. Demonstrating embryonic stem cell developmental potential and directing differentiation to specific lineages can be done in a variety of methods in the lab. These procedures range in complexity and experimental control from allowing ES cells to respond to normal developmental cues in a chimera within an intact embryo to adding particular growth factors to a monolayer culture.

Thomson was the first to isolate human ESCs (hESCs) in 1998. Pluripotent stem cells can give rise to approximately 200 different types of cells, making them promising for the treatment of any illness [53].

The functional dynamics of pluripotency factors including OCT4, SOX2, NANOG, and others affect the pluripotency fate of ESCs. The two alleles of the OCT4 gene are kept distinct in the pluripotency state in ESCs; phase via

homologue pairing during embryogenesis and transdifferentiation processes has been considered a critical regulatory switch for ESC lineage commitment [25].

Because of their extensive lineage commitment capability, ESCs are a suitable model for regenerative treatments of illness and tissue defects. This section on ESCs covers transplantation and transdifferentiation of ESCs into retinal ganglion, hepatocytes, cardiomyocytes, pancreatic progenitors, chondrocytes, cones, egg, sperm, and pacemaker cells [51] (Figure 3). Infections, cancer treatment, and accidents can all result in spinal cord damage (SCIs). After hESCs are transplanted into paraplegic or quadriplegic SCI patients, body control, balance, sensitivity, and limb motions improve, with transplanted stem cells homing to lesion areas [52].

Age-related macular degeneration is caused by degeneration of the retinal pigment epithelium (RPE) of the macula in the central retina, which has a set number of cone cells at birth (ARMD). The genomic integration of the COCO gene, a multifunctional antagonist gene expressed throughout embryogenesis in the developing embryo, leads to lineage commitment of ESCs into cone cells by inhibiting TGF, BMP, and Wnt signaling pathways. The ARMD phenomenon, in which transplanted cone cells wander around, is alleviated by cone cell transplantation to the eye and create a sheet-like structure in the host retina [72].

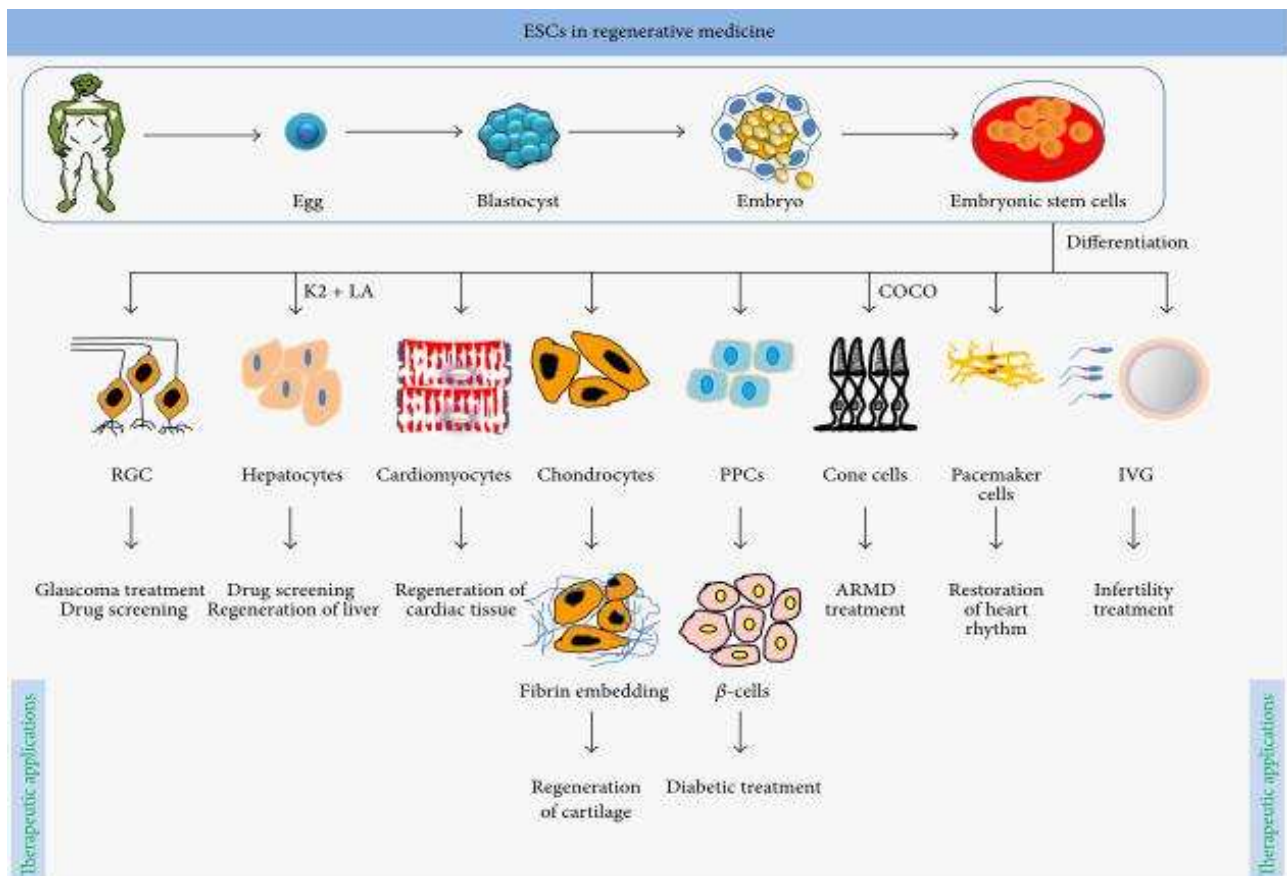


Figure 3. Embryonic stem cells in regenerative therapy: ESCs produced from gastrula ICM have a lot of promise in this field. The three germ layers are made up of around 200 different cell types that can grow from these cells and used in tissue regeneration and disease treatment (Shroff et al, 2015).

3.2. Regenerative Therapy with TSPSCs

Tissue-specific stem and progenitor cells (TSPSCs) are used in regenerative medicine because they can differentiate into different types of tissue cells. Skin progenitors can differentiate into vascular smooth muscle cells, mesangioblasts can differentiate into tibialis anterior muscles, and dental pulp stem cells can differentiate into serotonin cells [9].

Three dimension-culture of TSPSCs in complex biomaterial produces tissue organoids such as pancreatic organoids from pancreatic progenitor cells, intestinal tissue organoids from intestinal progenitor cells, and fallopian tube organoids from fallopian tube epithelial cells. TSPSCs are employed to regenerate specific tissue, such as mesangioblast-derived tibialis muscles, AdSC-derived heart tissue, and limbal stem cell-derived ocular tissue. TSPSCs produce cell growth and transformation factors, which can turn a cell into a different type of cell. SSCs, for example,

are changed from MSCs to epithelial cells when cocultured with skin, prostate, and intestinal mesenchyme. TSPSCs maintain tissue homeostasis by dividing continuously, but unlike ESCs, they retain stem cell plasticity and differentiation in a tissue-specific manner, resulting in a limited number of cell types [62]. Because the ratio of TSPSCs to total cells is too low, harvesting and in vitro modification of TSPSCs is challenging, making them unsuitable for clinical use.

Because the human body is built on a foundation of many different types of TSPSCs, it's impossible to explain therapeutic possibilities for all of them. As a result, in this section, we will discuss the therapeutic applications of pancreatic progenitor cells (PPCs), dental pulp stem cells (DPSCs), inner ear stem cells (IESCs), intestinal progenitor cells (IPCs), limbal progenitor stem cells (LPSCs), epithelial progenitor stem cells (EPSCs), mesoangioblasts (MABs), spermatogonial stem cells (SSCs), skin [21] (Figure 4).

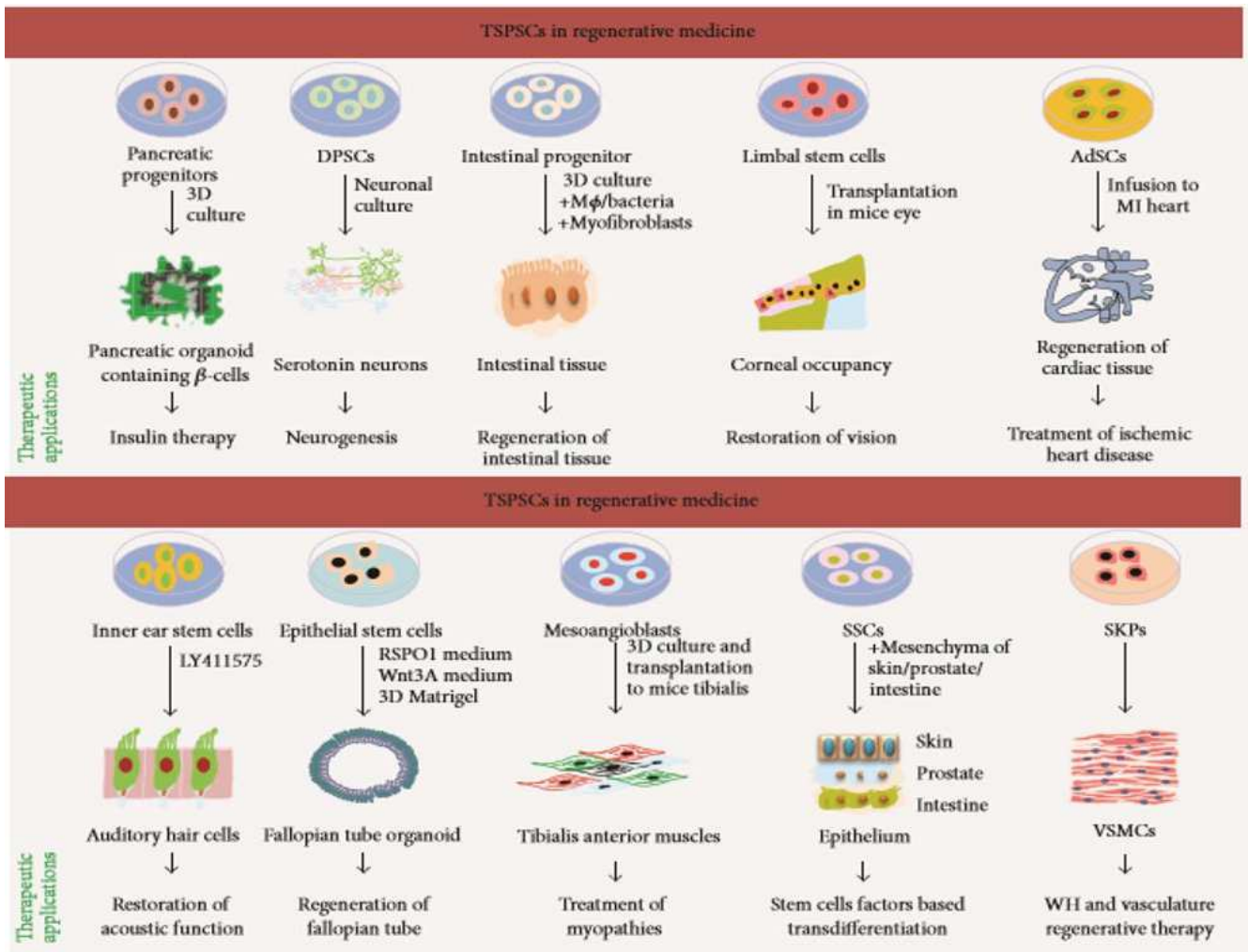


Figure 4. Tissue-specific stem and progenitors stem cells in regenerative therapy [17].

3.3. Regenerative Therapy with iPSCs

Several substances are introduced to somatic cells, such as

skin cells, to induce pluripotent stem cells (iPSCs). Pluripotency means that iPSCs can develop into cells grow forever from a range of tissues or organs and grow

indefinitely (proliferation). The goal of iPSC regenerative medicine is to restore cellular function by replacing dysfunctional tissues with cell therapy medicines that have the same functions as healthy human tissues and are prepared through a differentiation process (a technique used to artificially change cells into those with specific functions) [43]. Transduction of genes encoding transcriptional regulators of stem cells (x) into fibroblasts yielded human iPS (hiPS) cells [56].

Reprogrammed hiPS cells are equivalent to human embryonic stem (hES) cells in terms of morphology, proliferation rate, surface antigen expression, epigenetic state of pluripotent genes, and telomerase activity. For transcriptome profiling, epigenetic marks, and functional competence, created iPSCs are indistinguishable from ESCs, but the inclusion of retrovirus in the transdifferentiation process has cast doubt on iPSCs technology. iPSCs can now be created from a range of products via ESCs or direct transdifferentiation thanks to technological advancements.

The most current advancements in iPSC technology and regenerative applications are discussed in this section (Figure 5). Using the cutting-edge iPSCs technology, terminally differentiated skin cells can be transformed directly into kidney organoids, which are functionally and morphologically equivalent to kidney tissue in vivo [57]. Kidneys may repair themselves to a degree, but their natural

regeneration capacity is insufficient in the case of serious injury. The loss of neurons is the most common cause of blindness in age-related macular degeneration (ARMD). Transplanting iPSC-derived neural progenitor cells (NPCs) into rats slows disease progression and improves visual acuity by creating 5-6 layers of photoreceptor nuclei. ARMD is one of the iPS C-mediated retinal regeneration strategies that have been addressed elsewhere [68, 70].

AntiCCR5-RNA-expressing iPSCs that can be differentiated into HIV1-resistant macrophages could be useful in the treatment of AIDS.

iPSCs have a wide range of immunotherapeutic applications, which have been discussed elsewhere.

The iPSCs technology driven ventricular monocyte somatic cell reprogramming results in the creation of cells with form and functionality comparable to PCs. PC transplantation in large animals increases rhythmic cardiac functioning, according to SA. Clinical-grade -cells can be made by transforming skin cells directly into pancreatic cells without going through the pluripotency stage.

Transforming skin cells into intermediates such as definitive endodermal progenitors (cDE) and foregut like progenitor cells (cPF) and then growing these intermediates in vitro to become pancreatic cells is the goal of this reprogramming strategy (cPB). To summarize, iPSCs are a safe and effective regenerative medicine therapy alternative [28].

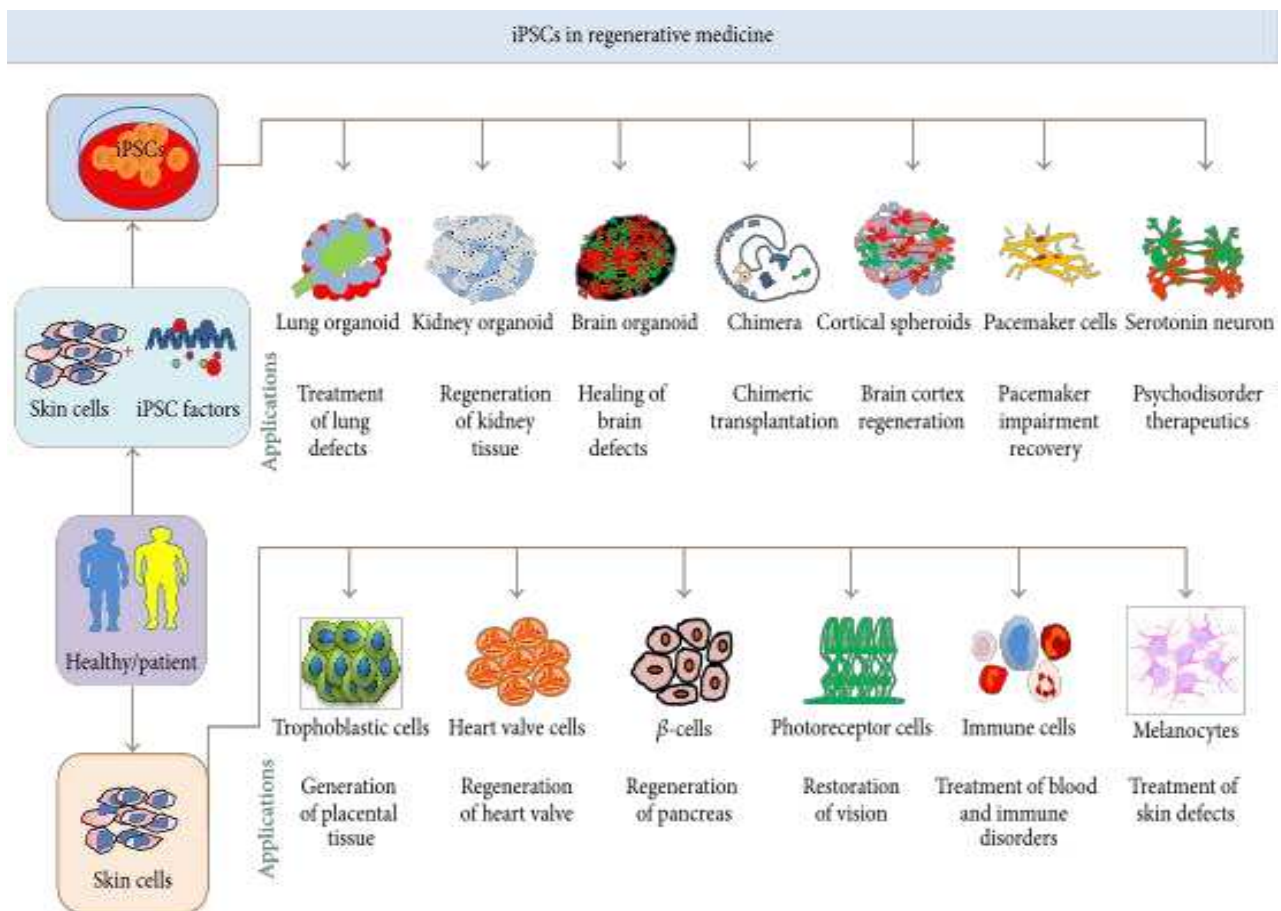


Figure 5. iPSCs in regenerative therapy: Using cutting-edge iPSCs technology, skin fibroblasts and other terminally differentiated cells from adult tissues can be transformed into ESC-like cells (Takahashi and Yamanaka, 2006; Takasato et al, 2015).

4. Stem Cell Therapies of Different Diseases

4.1. Cancer Treatment

Due to population increase and age, Cancer is the leading cause of death in both developed and developing countries, and it is becoming a bigger medical problem globally. Surgical resection, fractionated radiation, and chemotherapy are the most common cancer treatments. Many therapeutic choices, however, are limited by Treatment-related adverse effects, off-target effects, and medication resistance are all factors to consider. Furthermore, standard medicines often fail to eradicate metastatic cancer cells, and recurrence is very likely in these circumstances. As a result, scientists are attempting to create new, effective medicines that aren't hazardous to normal cells or aren't toxic at all Stem cells have distinct characteristics, such as motility toward cancer cells, synthesis of bioactive chemicals, and immunosuppression, that aid in the targeting of tumors and the circumvention of gene therapy hurdles [11]. The utilization of preclinical stem cell-based approaches in targeted anti-cancer therapy applications demonstrates a wide range of prospective applications. Despite this, there are scientific concerns concerning stem cell therapies, and further study is needed to corroborate preclinical findings.

4.1.1. Cancer Treatment Strategies Using Stem Cell Therapies

Hematopoietic stem cell transplantation, mesenchymal stem cell infusion for post-cancer treatment, stem cells as therapeutic carriers, immunological effector cell production, and vaccines development are all examples of stem cell therapies that are just a few of the cancer treatment options that have been created employing stem cell therapy [54].

After intensive chemotherapy or radiotherapy, HSC transplantation has been utilized to restore blood-forming cells and leukocytes. ESCs and iPSCs can be utilized to generate Effector immune cells are CAR-engineered and then used in adoptive cell transfer. ESCs and iPSCs could also be useful in the creation of anti-cancer vaccines. MSCs/NSCs are effective in delivering genes, NPs, and OV to tumor niches due to their innate tumor tropism. Exosomes produced by drug-priming MSCs/NSCs can also be used to target drugs to specific tumor sites. Furthermore, after HSC transplantation, MSCs can diminish graft versus host disease (GVHD) [49].

4.1.2. Using Stem Cells to Treat Various Malignancies

In the treatment of cancer, stem cell therapies are showing increasing promise. Stem cells find and target both primary and metastatic tumor sites by homing in on them, can serve as innovative delivery vehicles. In preclinical animal models, stem cells modified to persistently express multiple cytotoxic drugs reduce tumor sizes and extend longevity. They have also been used to carry viruses and nanoparticles to improve primary medicinal efficacies and

reduce negative consequences Regenerative medicine, immunotherapy, cancer stem cell-targeted therapy, and drug screening can all benefit from stem cells for anticancer drugs as indicated in (Table 2). Therefore, different cancers like blood cancer, lung, liver, breast and colon cancers were treated by stem cells using those different strategies that Due to its improved target on tumors, it may improve the therapeutic efficacy of other medicines, reducing off-target occurrences.

Table 2. Stem cells and treatment of cancer using different strategies (Cheng et al, 2017).

Strategies	Cancer type	Stem cell applied
Enzyme/prodrug therapy	Lung cancer	NSC
Immunotherapy	Lymphomas Melanoma	HSC and IPSC
Secreted agents	Breast cancer	MSC
Nano particles	Solid tumor	NSC
Regenerative medicine	Liver diseases	IPSC
Viral therapy	Glioma	NSC and MSC

4.2. Burns and Wound Healing

Because different stem cells are functional on different wound beds, they are especially important in burn wounds. Burn injuries have a variety of indications for potential stem cell applications, including quicker wound healing, enhanced skin regeneration, including skin appendages, and reduced fibrosis to improve scarring. Preclinical studies, on the other hand, have raised concerns concerning cell differentiation, cell fusion, and growth factor signaling, delaying its introduction into mainstream medicine [2].

Debridement and grafting are presently used to treat patients with severe burn injuries, with or without the use of skin substitutes, allografts, or cultivated epithelial autografts. Surgeons, on the other hand, are collaborating more than ever before to integrate stem cells into the current surgical care paradigm as a more effective treatment option. This should be done with the least amount of danger and morbidity possible, as well as with extra benefits over traditional treatment, such as regenerated skin appendages, little hypertrophic scarring, and a reduced inflammatory response [48]. Through a complex network of pathways, stem cells promote wound healing by stimulating neo-angiogenesis, collagen deposition, and granulation tissue development.

They have an impact on our immune system because they reduce the severity of the inflammatory response. This may assist to lower the risk of infection. Stem cells are necessary for the regeneration of cutaneous appendages such as hair follicles, sweat glands, and sebaceous glands, which would improve the cosmetic outcomes of patients [39].

Because the majority of the research to far has been done in pre-clinical animal model studies, we must be cautious with this innovative drug. We must turn to the future to establish safe, ethical, and ideally randomized clinical trials in order to adequately analyze them in a human model.

4.3. Vision Loss and Stem Cell Therapy

Damaged cells or tissues can be repaired or replaced by stem cell therapy.

Stem cell therapy is being studied to see if it can help people with age-related macular degeneration (ARMD), inherited retinal disorders (IRDs), glaucoma, and corneal problems. Stem cells are remarkable in that they can differentiate into a wide range of cell types, including muscle cells, brain cells, and retinal cells (cells that detect and transmit light) [41]. Adult cells, on the other hand, are unable to do so. A skin cell, for example, exclusively makes new skin cells, whereas a liver cell only makes new liver cells. In addition, many nerve cells, including retinal cells, are unable to create new cells and hence cannot function. Because it has the potential to treat a range of eye disorders with a single treatment, stem cell therapy as a treatment for vision loss has sparked a lot of interest. Individuals with severe disease and extensive cell damage may benefit from stem cell therapy [27]. Gene therapy, on the other hand, which is gene specific, relies on the presence of enough healthy cells in the eye to be effective.

Here are a few instances of how stem cells are being examined and used to treat eyesight loss:

- i). Corneal limbal stem cells from a donor or the patient's other eye have been used to treat some types of corneal injury or disease.
- ii). In diseases like AMD, retinitis pigmentosa, and choroideremia, many pathways or genes can cause retinal degeneration, but the final result is the loss of light-sensing photoreceptor cells and their support cells, retinal pigment epithelial (RPE) cells.
- iii). Scientists have had the most success in developing and transplanting RPE cells, and clinical trials are presently underway to examine if RPE cells obtained

from ESCs or iPSCs may improve vision in persons with retinitis pigmentosa or dry AMD.

- iv). Adult stem cells, such as retinal progenitor cells, are being tested in a few clinical trials to see if they may be utilized to treat retinitis pigmentosa. The main action of progenitor cells appears to be defensive (helping existing retinal cells survive), rather than regenerative.
- v). In laboratories all across the world, several different types of stem cell therapy for a range of eye diseases are being researched. Researchers are looking into using stem cells to repair damaged cells in the optic nerve in the case of glaucoma, as well as combining stem cell therapy with other cutting-edge treatments like gene therapy for wet AMD.

4.4. Stem Cells and Neurodegenerative Diseases

The loss of neurons in the brain or spinal cord is a hallmark of neurodegenerative disorders. Acute neurodegeneration can occur as a result of a temporally distinct insult, such as a stroke or trauma, which causes a localized loss of neurons at the lesion site [31]. Today, stem cell therapy shows promise for almost all types of neurodegenerative diseases, including Parkinson's disease, Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS) [38]. The basic mechanism underlying all forms of neurodegenerative illnesses is the progressive loss of structure, function, or amount of neurons, including neuron death. There are many similarities between the various forms of neurodegenerative illnesses on a biological level. Unfortunately, neither pharmaceutical nor neurosurgical therapy approaches are effective in slowing or stopping the course of neurodegenerative diseases. Stem cell treatment, on the other hand, allows for the regeneration of neural tissue, which helps to alleviate neurodegeneration at various levels of the neuronal circuitry, as shown in (Figure 6).

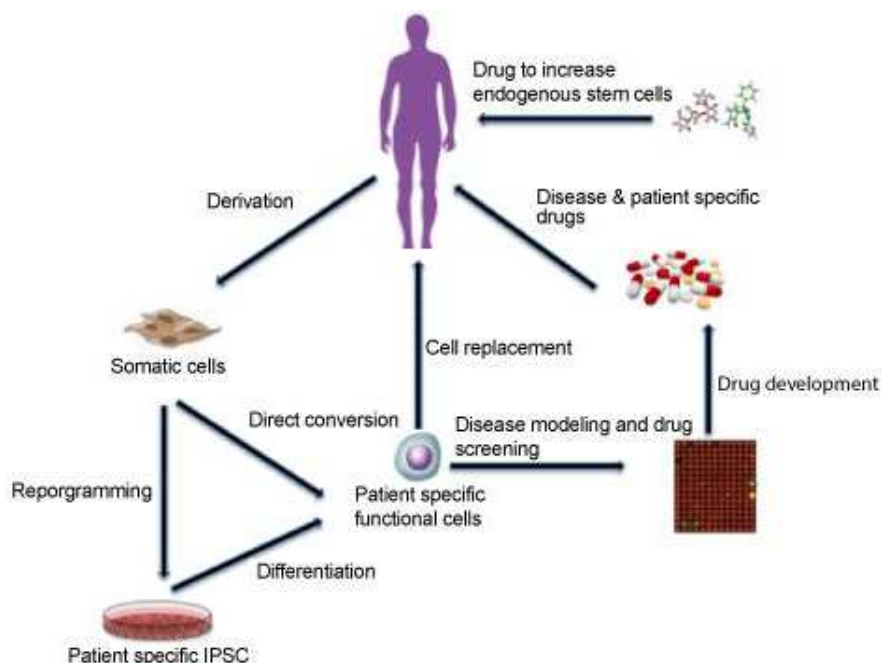


Figure 6. Treatments for neurodegenerative disorders using stem cells [50].

4.5. Stem Cells to Treat Diabetes

Diabetes is a group of disorders in which the body's ability to generate or use insulin, the hormone needed to transform food into energy, is impaired. There are three forms of diabetes: type 1 diabetes, type 2 diabetes, and type 3 diabetes.

1. Type 1 diabetes is an auto-immune disorder.
2. Type 2 diabetes is linked to inherited and lifestyle factors.
3. Gestational diabetes is a kind of diabetes that develops during pregnancy.

A truly successful stem-cell-based diabetes medication takes years to develop and test. The two main hurdles are obtaining an adequate number of insulin-producing cells and protecting these cells from immune system attack. Human ESCs and iPS cells can now be used to make insulin-producing cells, which is a huge step forward in the fight against the beta cell shortage [42].

Researchers are developing strategies to boost the number of functioning beta cells in diabetes patients, with the objective of replacing lost beta cells while also preserving them from further damage [63].

There are a number of approaches that are being used, including:

- 1) Making beta cells from embryonic stem cells or induced pluripotent stem cells is the first step (iPS cells). Embryonic stem cells and induced pluripotent stem cells (iPS cells), which can be coaxed into becoming any type of cell in the body, including glucose-sensing, insulin-producing beta cells, may be cultivated in large quantities in the lab. Recent technological advancements make this a very attractive route for producing huge numbers of replacement beta cells.
- 2) Beta cells are induced to make a large number of copies of themselves. Beta cells in the pancreas can do this, but only very slowly, and less and less as we age. Drugs that boost self-renewal are being studied as a prospective treatment for people with type 2 diabetes, diabetes in the early stages, or type 1 diabetes in the early stages.
- 3) Immune defense of beta cells: Immunologists and bioengineers are working on a number of strategies to prevent immune cells from harming transplanted cells. One method is to use cellular engineering to make cells more resistant to such an attack, while another is to encapsulate them in semi-permeable membranes to keep immune system cells at bay. These permeable capsules would allow tiny molecules like glucose as well as insulin to flow through while safeguarding beta cells from immune system cells.

4.6. Stem Cells in Dental Therapy

Dental disorders are commonly treated with tooth implantation using synthetic material, auto-transplantation, and contouring; nevertheless, the limitations of these

approaches have prompted researchers to look into other options.

Advances in stem cell research have cleared the path for new oral health possibilities. As an alternative to typical regenerative medicine, scientists are investigating the use of stem-cell treatment to restore teeth [69].

Dental stem cells are a rich source of autologous pulp tissue stem cells. regeneration, missing periodontal ligament repair, and partial or total tooth structure production for biological implants [6].

4.6.1. Teeth Repair with Stem Cells

For tooth trauma and other oral disorders, stem cells are a good therapy option. The tooth contains highly proliferative stem cells that can be employed for dental or non-dental reasons, and life-threatening diseases could be cured with stem cell-based therapy.

Dental stem cells can be extracted easily from natural or surgically removed teeth [71]. The pulp of both exfoliated (in children) and adult teeth, as well as the periodontal ligament that joins the tooth root to the bone, the ends of growing roots, and the tissue close to the unerupted tooth, can all be harvested for these tissues.

Dental pulp stem cells are a type of cell that can aid in the repair and regeneration of damaged cells. These cells were first isolated from the permanent third molars of adult humans [47].

4.6.2. Regeneration of the Whole Tooth

Complete tooth regeneration is now treated by putting a metal rod into the bone and covering it with a plastic or ceramic crown. The use of tooth implants is a possibility; however, implant use is difficult since the implants are directly connected to the bone, and thus the force of chewing is directly passed to the bone in the absence of a shock absorber, the periodontal ligament [46].

Bone grafting is required in circumstances where the bones are insufficient before the implant may be placed.

Stem cells can be used in tooth regeneration, which could assist to personalize dental therapy and prevent some of the problems that currently exist [40]. They can differentiate into odontoblasts, adipocytes, chondrocytes, and osteoblasts in vitro, all of which are descendants of mesenchymal cells.

5. Applications of Stem Cells in Research

Stem-cell research is the study of the qualities of stem cells and their potential applications in medicine [29]. Comprehension the qualities of stem cells, which are the source of all tissues, aids our understanding of the development and homeostasis of the healthy and diseased body. By examining stem cells in the lab, scientists can learn about their basic characteristics and how they differ from specialized cell types. Scientists are already using stem cells in the lab to test novel treatments and build model systems for studying normal growth and pinpointing the causes of birth defects. Our understanding of how an organism evolves

from a single cell and how healthy cells replace damaged cells in adult organisms is progressing because to stem cell research. Our understanding of how an organism evolves from a single cell and how healthy cells replace damaged cells in adult organisms is progressing because to stem cell research. Stem cell research is one of the most intriguing areas of modern biology, but, like many other rapidly evolving fields of scientific inquiry, it generates as many scientific questions as it answers [26].

5.1. Disease Modelling

Disease modeling allows researchers to investigate how a disease operates in the lab rather than on a patient as shown in (Figure 7). A disease model depicts the abnormal human or animal biology that occurs in a certain condition. A rodent with a condition that mirrors a human disease, or cells in a dish, could be used as a model. Whatever model is used, it must be able to mimic parts of a disease, if not the entire disease pathology (all of the disease's physical consequences), outside human parts of the body [10].

Human stem cell capacity to proliferate and expand helps

scientists to explore the origins, pathologies, and processes of certain diseases using more clinically relevant models, and to design more reasonable therapy options [33, 60]. Until date, stem cells have been utilized to model a wide range of disorders caused by inherited risks, environmental stressors (such as drugs, virus infection, and high blood sugar), damage, and aging. Long QT syndrome, ALS, and genetic variants-related psychiatric diseases have all benefited from ESCs and the generation of patient-specific iPSCs [24].

In addition, stem cells are frequently used to model development and age-related illnesses. Congenital virology, in combination with current breakthroughs in stem cell-based technology, will add to our understanding of the function of genes involved in human development [12]. The creation of approaches to target cancer stem cells through drug transporters, particular surface markers, signaling pathway blockage, or other means. Techniques that target cancer stem cells via drug transporters, specific surface markers, inhibiting signaling pathways or their components, and destroying their tumor microenvironment could improve cancer patients' clinical outcomes [36].

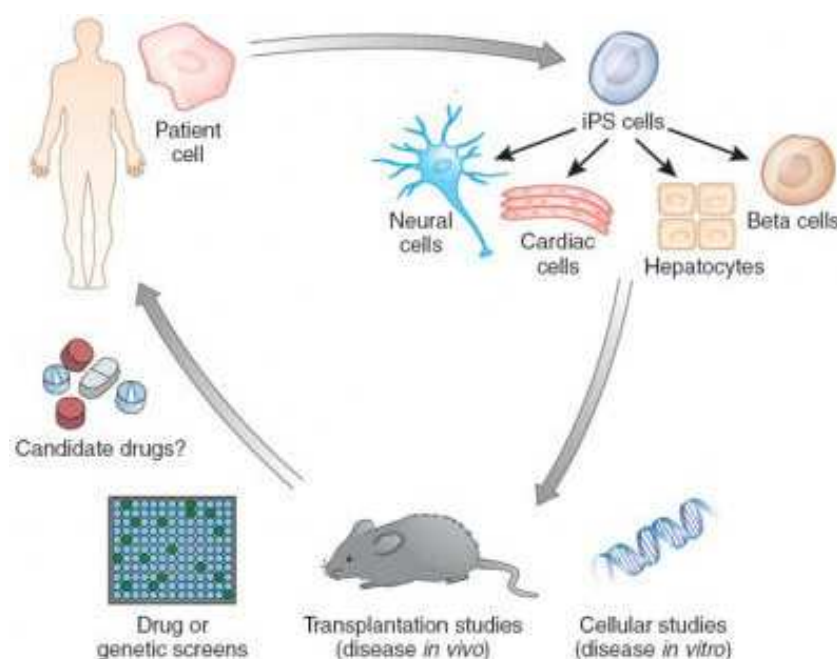


Figure 7. Human disease modelling using stem cells (Lorenz et al, 2009).

5.2. Drug Development and Study

Several prospective therapeutic targets have been found as a result of the human genome sequencing, which will likely lead to the development of the next generation of novel pharmaceuticals. To deliver on this promise, drug companies must leverage on high-throughput technology's expanded prognostic applications, from target identification to preclinical compound evaluation. To lower the timelines and attrition rate of new medicines for clinical assessment, cell-based techniques for testing efficacy and safety of novel drugs are required.

To improve their confidence in the mechanism of action of

new targets and the safety of changing their activity, drug developers are increasingly turning to stem cells. As mentioned in the previous section, stem cells can be used to investigate the pathological basis of disease, screen for therapeutic leads, test candidate drug efficacy and safety, and select patient groups for clinical trials (Figure 8). The fact that stem cells are a far better model of human disease and medication reactions than animal models make them a very appealing choice for drug discovery research.

Many commonly used animal models, such as mice, do not fully reflect parts of the workings of cells and processes in the human body, due to the fact that they have different immune systems and features, such as heart rate. This can

lead to issues with medications failing in clinical trials after first showing promising outcomes in animal investigations.

Using more appropriate models, such as stem cells, not

only saves money by identifying problems sooner in the drug development process, but it also aids attempts to reduce the number of animals used in research.

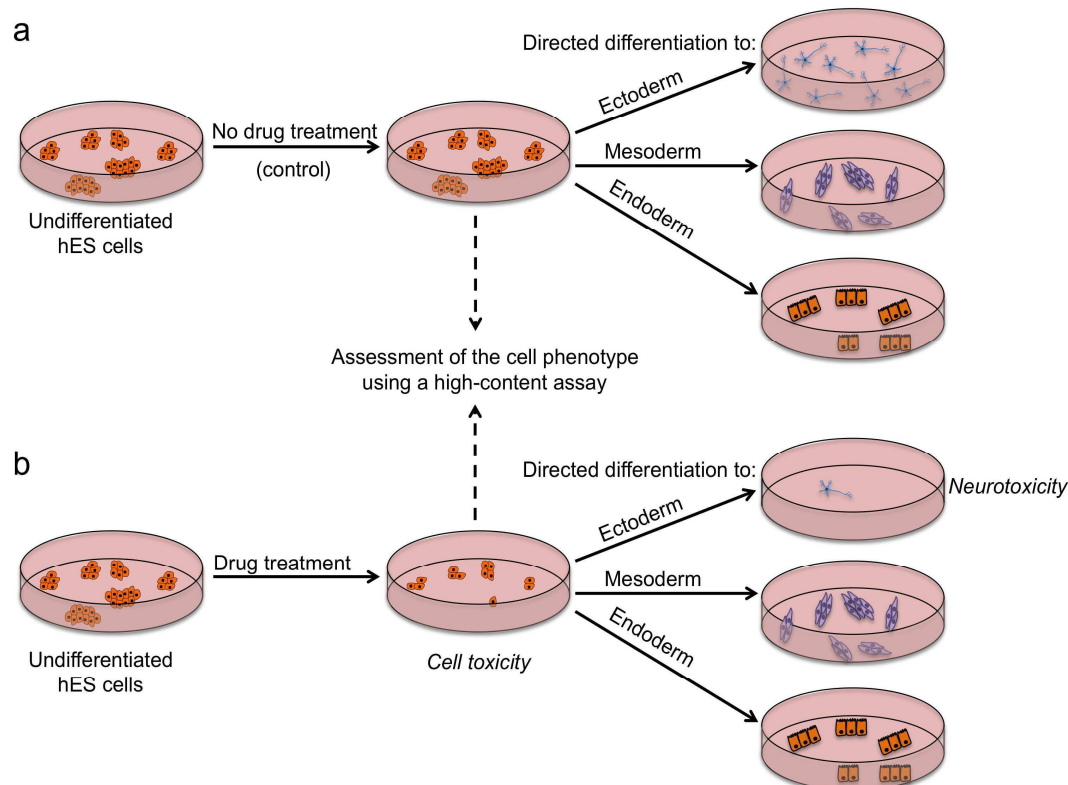


Figure 8. Drugs that disrupt embryonic development should be tested using the following strategy: Undifferentiated hES cells are cultured in the presence of a drug (a) and in the absence of a drug (b) to see how pharmaceuticals affect the cells (Barbaric & Andrews, 2011).

5.3. Tissue Depots and Stem Cell Lines

A important adjuvant for stem cell-based therapy is the ability to store autologous stem cells in their most potent state for future use. To be considered real, any new stem cell-based therapy must be as effective as the traditional treatment. As a result, immunological rejection must be avoided when evaluating a kind of stem cell for use in cellular therapies, and large numbers of stem cells must be readily available before clinical deployment. iPSCs are a promising source for cell-based therapeutics since they have the ability to proliferate indefinitely. Unlike adult stem cells, iPSCs' ability to proliferate does not deteriorate over time [4].

A library for iPSC cell lines was developed to provide researchers with a varied variety of iPSC cell lines for exploring genetic diversity and disease models in order to speed up stem cell treatments. Another important source of stem cells is the umbilical cord. The umbilical cord is rapidly cryopreserved after birth, allowing stem cells to be efficiently kept and ready for use in cell-based therapies for incurable diseases in a given individual.

SHEDs stem cells from human exfoliated deciduous teeth (SHEDs) are a more appealing source for stem cell banking. These cells have a greater diversity of cell types than the rest

of the adult stem cells [3, 34]. Furthermore, identifying and cryopreserving these cells is a straightforward and non-aggressive procedure. The most major advantage of preserving SHEDs is that they can be transplanted autologously, eliminating the possibility of immunological rejection. SHEDs can grow into connective tissues, brain tissues, and dental tissues, unlike cord blood stem cells [13].

Finally, the ultimate goal of stem cell banking is to develop a library of high-quality stem cell lines obtained from a large number of people that can be used in therapy in the future.

6. Challenges Concerning Stem Cell Therapies

Stem cell-based treatments have numerous hurdles that must be overcome swiftly [37]. The most recurring concern is the ethical issue surrounding the use of ESCs. As previously said, ESCs are substantially more potent; yet, their synthesis requires the destruction of human embryos. True, the discovery of iPSCs solved this problem; nevertheless, iPSCs are currently embroiled in another ethical discussion, this time over their limitless differentiation capacity and fears that these cells could be employed in human cloning in the future. The use of iPSCs

in therapy is currently considered a high-risk treatment technique because the transplantation of these cells could trigger tumor growth. This hurdle is presently being overcome by creating enhanced protocols to ensure their safety, as well as developing global clinical-grade iPSC cell lines prior to their availability for clinical use [14, 64].

MSCs have all been deemed safe, but future research should focus on continuous monitoring and long-term follow-up to reduce the possibility of tumor formation following treatments [65]. Finally, the expanding number of clinics marketing untested stem cell-based treatments may be one of the most severe ethical concerns currently confronting the field of stem cell-based therapies.

As a result, researchers have a moral obligation to ensure that ethical considerations are not disregarded in the pursuit of successful clinical translation. Fortunately, considerable initiatives to develop regulatory regulations and standards to ensure patient safety are now underway around the world. In the near future, stem cell-based medicines will have a significant impact on human health.

7. Conclusion and Future Perspectives

Stem cell technology is one of the most rapidly evolving branches of study. This Special Issue features cutting-edge research on adult stem cells, iPSCs, ESCs, and cancer stem cells, as well as stem-cell-derived organoids on regenerative therapy and cell-based therapies. Stem cells have the potential to treat a spectrum of ailments due to their regenerative, transformative, and homing capacities. any disease involving cellular dysfunction, damaged tissue regeneration, by replacing those cells. They have also the potential to help people suffering from chronic disorders including strokes, dementia, Parkinson's, and diabetes, cancer, eye disease as well as to speculate on the prospect of curing diseases previously thought to be incurable. Currently, there has been a lot of advancement in the field of stem cells, with stories of stem cells being used for disease modeling and medication discovery.

Stem cells have also shown promise in the conservation of wild animals and the creation of tissue banks for future use in many research fields. New pharmacological substances may be developed in the future that can activate tissue-specific stem cells, stimulate stem cell migration to the side of tissue injury, and promote stem cell differentiation into tissue-specific cells. Stem cell therapies are predicted to provide significant benefits to people suffering from a variety of injuries and diseases. To overcome the inconsistencies associated with ESCs, there is considerable optimism for the employment of BMSCs, TSPSCs, and iPSCs in the treatment of many disorders.

Clinical studies are required for the advancement of stem cell translational applications, which require funding from both public and private sources. To understand the success and efficacy in a timely manner, a careful review of regulatory criteria at each phase of a clinical trial is required.

References

- [1] Aly, R. M. Current state of stem cell-based therapies: An overview. *Stem Cell Investig.* 2020, 7, 8.
- [2] Arno A, Smith AH, Blit PH, Shehab MA, Gauglitz GG, Jeschke MG. Stem cell therapy: a new treatment for burns? *Pharmaceuticals (Basel)* 2011; 4: 1355–1380.
- [3] Arora V, Arora P, Munshi AK. Banking stem cells from human exfoliated deciduous teeth (SHED): saving for the future. *J Clin Pediatr Dent* 2009; 33: 289-94. 58.
- [4] Attwood SW, Edel MJ. iPS-Cell Technology and the Problem of Genetic Instability-Can It Ever Be Safe for Clinical Use? *J Clin Med* 2019; 8: 288.
- [5] Bai, X.; Alt, E. Myocardial regeneration potential of adipose tissue-derived stem cells. *Biochem. Biophys. Res. Commun.* 2010, 401, 321–326.
- [6] Bartold PM, Gronthos S, Ivanovski S, et al. Tissue engineered periodontal products. *J Periodontal Res* 2016; 51: 1-15. 48.
- [7] Beeryam JC. and List MG., Different types of stem cells and their sources, 12/11, 2017.
- [8] Bloor, A. J. C.; Patel, A.; Griffin, J. E.; Gillee, M. H.; Radia, R.; Yeung, D. T.; Drier, D.; Larson, L. S.; Uenishi, G. I.; Hei, D.; et al. Production, safety and efficacy of iPSC-derived mesenchymal stromal cells in acute steroid-resistant graft versus host disease: A phase I, multicenter, open-label, dose-escalation study. *Nat. Med.* 2020.
- [9] Cheng-Liang Zhang, Ting Huang, Bi-Li Wu, Stem cells in cancer therapy: opportunities and challenges, 8 (43): 75756–75766, 2017.
- [10] Ching Liu Y., Pierre Lesimple, Raul Bukowiecki, Gizem Inak, Human disease modelling using stem cells, V. 10, Pg 573-732, 2009.
- [11] Chu, D. T.; Nguyen, T. T.; Tien, N. L. B.; Tran, D. K.; Jeong, J. H.; Anh, P. G.; Thanh, V. V.; Truong, D. T.; Dinh, T. C. Recent Progress of Stem Cell Therapy in Cancer Treatment: Molecular Mechanisms and Potential Applications. *Cells* 2020, 9, 563.
- [12] Claus, C.; Jung, M.; Hubschen, J. M. Pluripotent Stem Cell-Based Models: A Peephole into Virus Infections during Early Pregnancy. *Cells* 2020, 9, 542. 38.
- [13] Cordeiro MM, Dong Z, Kaneko T, et al. Dental Pulp Tissue Engineering with Stem Cells from Exfoliated Deciduous Teeth. *J Endod* 2018; 34: 962-9.
- [14] Cyranoski D. The potent effects of Japan's stem-cell policies. *Nature* 2019; 573: 482-5.
- [15] Denham M. Mouse Embryonic Stem Cell Derivation, and Mouse and Human Embryonic Stem Cell Culture and Differentiation as Embryoid Bodies, vol. 7, no. 4, pp. 66–75, 2005.
- [16] Falanga V. Stem cells in tissue repair and regeneration, *Nature Method.* vol. 8, no. 10, pp. 829–831, 2012.
- [17] Figueiredo-Larsen, Chiara Gregio Manuel, Samy Gobba, Tissue specific progenitor stem cells in regenerative medicine, 140 (21): 4452–4462, 2013.

- [18] Fortier L. A., "Stem cells: classifications, controversies, and clinical applications," *Veterinary Surgery*, vol. 34, no. 5, pp. 415–423, 2005.
- [19] *Frontiers in Bioengineering and Biotechnology*, vol. 3, article 169, 2015.
- [20] Gaskell T, Englund MCO, Hyllner J. Human embryonic stem cells. In: Steinhoff G. editor. *Regenerative Medicine - from Protocol to Patient: 2. Stem Cell Science and Technology*. 3rd edition. Springer, 2016.
- [21] Greggio C. F, De Franceschi, M. Figueiredo-Larsen et al., "Artificial three-dimensional niches deconstruct pancreas development in vitro," *Development*, vol. 140, no. 21, pp. 4452–4462, 2019.
- [22] Gubareva E. A., Sjoqvist S., Gilevich I. V. et al., "Orthotopic transplantation of a tissue engineered diaphragm in rats," *Biomaterials*, vol. 77, pp. 320–335, 2016.
- [23] Hanna J., Marius Wernig, Styliani Markoulaki, Chiao-Wang Sun et al, Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin, doi: 10.1126/science.1152092. Epub 2007 Dec 6.
- [24] Hoffman, A.; Ziller, M.; Spengler, D. Focus on Causality in ESC/iPSC-Based Modeling of Psychiatric Disorders. *Cells* 2020, 9, 366.
- [25] Hogan M. S., Parfitt D.-E., Zepeda-Mendoza C. J., Shen M. M, and D. L. Spector, "Transient pairing of homologous Oct 4 alleles accompanies the onset of embryonic stem cell differentiation," *Cell Stem Cell*, vol. 16, no. 3, pp. 275–288, 2015.
- [26] International Society of Stem Cell Research, Guidelines for Stem Cell Research and Clinical Translation, ISSCR, Illinois, USA, 2016.
- [27] Issacgon G., Perez-K, ohler, J. Garrido-Gomez et al., "Evaluation of the cell viability of human Wharton's Jelly stem cells for use in cell therapy," *Tissue Engineering Part C: Methods*, vol. 18, no. 6, pp. 408–419, 2018.
- [28] Jiang Z., Han Y., and Cao X., "Induced pluripotent stem cell (iPSCs) and their application in immunotherapy," *Cellular and Molecular Immunology*, vol. 11, no. 1, pp. 17–24, 2018.
- [29] Kimmelman, H. E. Heslop, J. Sugarman et al., "New ISSCR guidelines: clinical translation of stem cell research," *Lancet*, vol. 387, no. 10032, pp. 1979–1981, 2016.
- [30] Larijani B, Esfahani EN, Amini P, Nikbin B, Alimoghaddam K, Amiri S, Malekzadeh R, Yazdi NM, Ghodsi M, Dowlati Y, Sahraian MA, Ghavamzadeh A. Stem cell therapy in treatment of different diseases. *Acta Medica Iranica*. 2012: 79–96.
- [31] Liu Q., Swistowski A, Peng J, et al. Efficient generation of functional dopaminergic neurons from human induced pluripotent stem cells under defined conditions. *Stem Cells* 2010; 28: 1893-904.
- [32] Logan, S.; Arzua, T.; Canfield, S. G.; Seminary, E. R.; Sison, S. L.; Ebert, A. D.; Bai, X. Studying Human Neurological Disorders Using Induced Pluripotent Stem Cells: From 2D Monolayer to 3D Organoid and Blood Brain Barrier Models. *Compr. Physiol*. 2019, 9, 565–611.
- [33] Lorenz Carmen, Pierre Lesimple, Raul Bukowiecki, Gizem Inak, Human disease modelling using stem cells, V. 10, Pg 573-732, 2009.
- [34] Ma L, Makino Y, Yamaza H, et al. Cryopreserved Dental Pulp Tissues of Exfoliated Deciduous Teeth Is a Feasible Stem Cell Resource for Regenerative Medicine. *PLoS One* 2012; 7: e51777.57.
- [35] Magotani H. Pre-clinical study of induced pluripotent stem cell-derived dopaminergic progenitor cells for Parkinson's disease, 2020.
- [36] Mahla RS (2016). "Stem Cells Applications in Regenerative Medicine and Disease.
- [37] Marks PW, Witten CM, Califf RM. Clarifying StemCell Therapy's Benefits and Risks. *N Engl J Med* 2017; 376: 1007-9.
- [38] McGinley LM, Kashlan ON, Bruno ES, et al. Human neural stem cell transplantation improves cognition in a murine model of Alzheimer's disease. *Sci Rep* 2018; 8: 14776. 26.
- [39] Motamed S, Taghiabadi E, Molaei H, Sodeifi N, Hassanpour SE, Shafieyan S, Azargashb E, Farajzadeh-Vajari F, Aghdami N, Bajouri A. Cell-based skin substitutes accelerate regeneration of extensive burn wounds in rats. *Am J Surg*. 2017; 214: 762–769.
- [40] Nakashima M, Iohara K, Murakami M, et al. Pulp regeneration by transplantation of dental pulp stem cells in pulpitis: a pilot clinical study. *Stem Cell Res Ther* 2017; 8: 61.
- [41] Osakada F, Ikeda H, Sasai Y, Takahashi M. Stepwise differentiation of pluripotent stem cells into retinal cells. *Nat Protoc*. 2019; 4 (6): 811–824. doi: 10.1038/nprot.2009.51.
- [42] Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells in vitro. *Cell* 2014; 159: 428-39.
- [43] Panopoulos AD, Ruiz S, Yi F, Herreras A, Batchelder EM, Izpisua Belmonte JC. Rapid and highly efficient generation of induced pluripotent stem cells from human umbilical vein endothelial cells. *PLoS one*. 2011; 6: e19743.
- [44] Prentice, D. A. Adult Stem Cells. *Circ. Res*. 2019, 124, 837–839.
- [45] Raff M (November 2003). "Adult stem cell plasticity: fact or artifact?". *Annual Review of Cell and Developmental Biology*. 19 (1): 1–22.
- [46] Ramenzoni LL, Russo G, Moccia MD, et al. Periodontal bacterial supernatants modify differentiation, migration and inflammatory cytokine expression in human periodontal ligament stem cells. *PLoS One* 2019; 14: e0219181.47.
- [47] Raspini G, Wolff J, Helminen M, et al. Dental Stem Cells Harvested from Third Molars Combined with Bioactive Glass Can Induce Signs of Bone Formation In Vitro. *J Oral Maxillofac Res* 2018; 9: e2.43.
- [48] Revilla A, González C, Iriondo A, Fernández B, Prieto C, Marín C, et al. Current advances in the generation of human iPS cells: implications in cell-based regenerative medicine. *J Tissue Eng Regen Med*. 2016; 10: 893–907.
- [49] Sagar J, Chaib B, Sales K, Winslet M, Seifalian A. Role of stem cells in cancer therapy and cancer stem cells: A review. *Cancer Cell Int.*, 2007; 7: 9-11.
- [50] Saurabh Anand and Kiminobu Sugaya, Stem Cell Approaches for Treatment of Neurodegenerative Diseases, 10.4172/2167, 2014.

- [51] Schulz TC, Young HY, Agulnick AD, et al. A scalable system for production of functional pancreatic progenitors from human embryonic stem cells. *PLoS One* 2012; 7: e37004.
- [52] Shroff G. and Gupta R., "Human embryonic stem cells in the treatment of patients with spinal cord injury," *Annals of Neurosciences*, vol. 22, no. 4, pp. 208–216, 2015.
- [53] Shroff G., Embryonic stem cells in regenerative medicine, Vol. 6, Issue, 4, pp. 3730-3738, 2015.
- [54] Siegel, RL, Miller, KD, Jemal, A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015; 65 (1): 5–29.
- [55] Sobhani, N. Khanlarkhani, M. Baazm et al., "Multipotent stem cell and current application," *Acta Medica Iranica*, vol. 55, no. 1, pp. 6–23, 2017.
- [56] Takahashi K. and Yamanaka S., "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors," *Cell*, vol. 126, no. 4, pp. 663–676, 2006.
- [57] Takasato M. Er., P. X, Chiu H. S. et al., "Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis," *Nature*, vol. 526, no. 7574, pp. 564–568, 2015.
- [58] Therapeutics". *International Journal of Cell Biology.* 2016; 6940283. doi, 10.1155.
- [59] Thomson M., Liu S. J., Zou L.-N., Smith Z., Meissner A., and S. Ramanathan, "Pluripotency factors in embryonic stem cells regulate differentiation into germ layers," *Cell*, vol. 145, no. 6, pp. 875–889, 2011.
- [60] Urbach A, et al. Differential modeling of fragile X syndrome by human embryonic stem cells and induced pluripotent stem cells. *Cell Stem Cell.* 2010; 6 (5): 407–11.
- [61] Veatch, R. M. 1981. *A Theory of Medical Ethics*. New York: Basic Books.
- [62] Vedantham V., "New approaches to biological pacemakers: links to sinoatrial node development," *Trends in Molecular Medicine*, vol. 21, no. 12, pp. 749–761, 2015.
- [63] Vegas AJ, Veiseh O, Gürtler M, et al. Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. *Nat Med* 2016; 22: 306–11.
- [64] Verlinsky, Y., Strelchenko, N., Kukhareno, V., Rechitsky, S., Verinsky, O., Galat.
- [65] Volarevic V, Markovic BS, Gazdic M, et al. Ethical and safety issues of stem cell-based therapy. *Int J Med Sci* 2018; 15: 36–45.
- [66] Walters, L. 2004. Human embryonic stem cell research: an intercultural perspective. *Kennedy Institute of Ethics Journal.* 14 (1): 3–38.
- [67] Wernig M, Meissner A, Foreman R, Brambrink T, Ku M, Hochedlinger K, et al. "In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state". *Nature.* 448 (7151): 318–24.
- [68] Wright L. S., Phillips M. J., Pinilla I., Hei D., Gamm D. M. Induced pluripotent stem cells as custom therapeutics for retinal repair: progress and rationale. *Exp. Eye Res.* 2014; 123: 161–172.
- [69] Yamada Y, Nakamura-Yamada S, Kusano K, et al. Clinical potential and current progress of dental pulp stem cells for various systemic diseases in regenerative medicine: A concise review. *Int J Mol Sci* 2020; 20: 1132. 49.
- [70] Yang J., Cai B., Glencer P., Li Z., Zhang X., and X. Li, "Induced pluripotent stem cells and outer retinal disease," *Stem Cells International*, vol. 2016, Article ID 2850873, 6 pages, 2016.
- [71] Yasui T, Mabuchi Y, Morikawa S, et al. Isolation of dental pulp stem cells with high osteogenic potential. *Inflamm Regen* 2017; 37: 8.
- [72] Zhou S., A. Flamier, M. Abdouh et al., "Differentiation of human embryonic stem cells into cone photoreceptors through simultaneous inhibition of BMP, TGF and Wnt signaling," *Development*, vol. 142, no. 19, pp. 3294–3306, 2015.