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STEM CELL - A HOPE FOR FUTURE HEALTHCARE SECTOR

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ABSTRACT: Stem cell-based therapeutics have considerable potential to treat a variety of illnesses that are now incurable. Because of recent scientific advancements, the area of applied medical research has taken a positive turn, and stem cell-based techniques have moved considerably closer to clinical applications. Since their discovery, stem cells have revolutionized medical research and dramatically altered our understanding of human biology. Understanding of the evolution of the human body and how it fixes itself after harm has been greatly increased. This is why the use of stem cells in human applications has expanded dramatically. This has boosted interest in stem cell therapy. With a genuine interest in long-term quality research into critical problems, some of which are described below, it will be intriguing to deliver therapies based on stem cells to patients with terminal diseases and impairments in order to assist them significantly enhance their quality of life. Stem cell treatments have emerged as a promising and advanced area in scientific study in recent years. This advancement has increased the bar for the treatment of fatal illnesses. This research examines the many kinds of stem cells and their possible therapeutics. This study focuses on the scientific foundations, present scenarios, and clinical applications of stem cells in the treatment of numerous currently incurable diseases, as well as future advances in our health care industry.

INTRODUCTION: Stem cells are the cells of the human body that are unspecialized and have the ability to differentiate into many different cell types of an organism. These cells also possess characteristics of self-renewal [1, 2]. There are many potential sources from which different stem cells can be derived. Some of these sources include embryonic stem cells (ESCs), fetal stem cells (FSCs), neural stem cells (NSCs), umbilical cord stem cells (UCSCs), adult stem cells, and mesenchymal stem cells (MSCs).

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Based on their differentiation abilities, human embryonic stem cells are categorized into totipotent, pluripotent, multipotent, oligopotent, and unipotent [3] **Table 1.** Totipotent stem cells are those stem cells that have the highest differentiation potential and possess the ability to divide and differentiate into an embryo which can lead to a whole new individual and all the different cell types of an organism.

An example of a cell that possesses totipotency is a zygote that is formed during fertilization between a sperm and an egg [1]. Embryonic stem cells can be isolated from the inner cell mass (ICM) of a developing blastocyst (approximately after 4 days) and are pluripotent, having the potential to give rise to all three germ layers - ectoderm, mesoderm, and endoderm [4]. Pluripotent stem cells can differentiate

into all types of cells but not into an embryo. Another example of stem cells showing pluripotency is induced pluripotent stem cells (iPSCs) that are artificially produced from somatic cells like fibroblasts or epiblast layer of implanted embryo[5] and are reprogrammed into cells similar to embryonic cells with the help of selected transcription factors like Oct4, Sox2, Klf4 and c-Myc [6-9]. These cells function like other pluripotent stem cells. These iPSCs provide a promising option for regenerative medicine for both, at present and also for the future because stem cells that occur naturally exhibit various limitations which motivated scientists to develop cells with increased levels of pluripotency [10, 11].

Multipotent stem cells can differentiate into some of the specific types of cells from which they can be obtained from a human body. There are various sources for multipotent stem cells: fetal organs containing fetal stem cells (FSCs) [12] neural stem cells (NSCs) that have the potential to differentiate into those types of cells that are within a neural lineage [13]. Adult stem cells are cells that can be isolated from the mature tissues of an organism [14]. A type of human adult stem cell is a hematopoietic stem cell (HSC) that can show differentiation into different blood cells types (red blood cells, white blood cells, and platelets) and because of their ability to give rise to limited types of cells, these also come under the category of multipotent stem cells. But after a hematopoietic stem cell is differentiated into a specific type of blood cell, it becomes oligopotent [1].

This restricts their differentiation ability to only the cells of their lineage. Oligopotent stem cells can differentiate into only a few types of cells. An example can be a myeloid stem cell which can develop into a leukocyte but not an erythrocyte. As a human keeps on developing, the differentiation ability of stem cells also gets reduced from totipotency to pluripotency and then into multipotent stem cells. An alternative to multipotent stem cells is mesenchymal stem cells (MSCs) [15, 16] which can be derived from adult bone marrow. These bone marrow cells (BMCs) can naturally develop into osteoblasts, chondrocytes, tenocytes, skeletal myocytes, and adipocytes [1, 17]. MSCs can also differentiate into bone, cartilage, muscle, fat and other connective tissues.

Reports and studies are suggesting their trans-differentiation into cells of neural lineages as well [18]. Several research works have resulted in some types of adult stem cells that have shown the capacity to develop into specialized cells which can be found in various organs or tissues different from the predicted lineage of a cell *i.e.* brain stem cells can develop into hemocytes that transform into heart cells, and so on. This is termed *trans-differentiation.* The differentiation pathways of various stem cells are different **Table 2.**

The reducing differentiating ability of a human finally gives rise to a unipotent stem cell. Unipotent stem cells are characterized by the narrowest ability to divide and differentiate and have the capability to form only one type of cell along with a unique property of repeated division. The latter feature gives them a promising ability for therapeutic use in regenerative medicine. Only one type of cell can be formed from these cells, e.g. dermatophytes.

From Basic Biology to Clinical Application: Studying the biology of different types of stem cells and using these cells in a clinical context by following the protocols of cell-based therapies is an exciting field of experimental research. With their interesting characteristic properties, these cells are expected to provide a new approach to the treatment of various chronic diseases **Fig. 1.**

Cell replacement therapy is a well-known strategy for the therapeutic application of stem cells. This involves the ability of stem cells to differentiate into a desired type of cell and then transport it to the damaged tissue. This allows the cells to integrate and restore functions. Extensive research works on various stem cell types during the last few decades have contributed a lot to the field of regenerative medicine and also to cancer therapies having the capability to produce multiple therapeutically useful types of cells which can further be used in treating numerous genetic and degenerative disorders.

Aging problems, blood or immune system-related disorders, cardiac diseases, diabetes, neurodegenerative diseases, arthritis, skin, lung, and retinal disorders as well as cancers are a few problems that can be addressed using therapies based on stem cells.

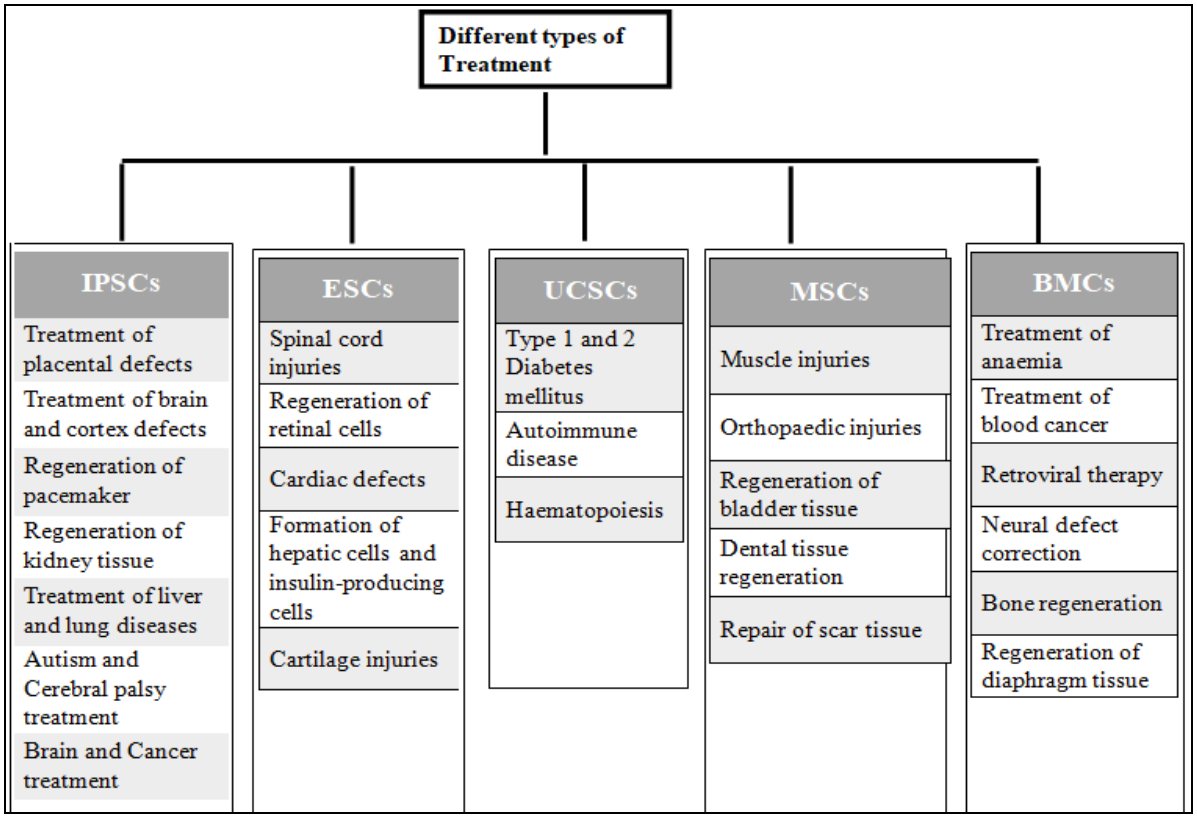

FIG. 1: TREATMENT OF DIFFERENT DISORDERS BY VARIOUS STEM CELLS

TABLE 1: CLASSIFICATION OF STEM CELLS BASED ON THEIR POTENTIAL TO DIFFERENTIATE

Types of stem cell	Developmental potency	Examples
Totipotent	Capable of differentiation into all cellstypesand even into a functional organism	Only the zygote and the first cleavage blastomeres.
Pluripotent	Capable of differentiation into almost all cells types but not into an organism	Embryonic stem cells. (Bain *et al.*, 1995, Odorico *et al.*, 2001)
Multipotent	Has the ability to develop into cells, but of related types	Adult Stem Cells, Mesenchymal Stem Cells. (Rubinstein *et al.*, 1993, Nishida *et al.*, 1999, Pittenger *et al.*, 1999, Mueller and Glowacki, 2001, Stenderup *et al.*, 2003)
Oligopotent	Has the ability to develop into cells, but only of certain types	Lymphoid or Myeloid Stem Cells
Unipotent	Capable of differentiation into cells, but only of its type. These cells also possess the capacity to self-renew which is essential for them to be called stem cells	Epithelial Stem Cells

TABLE 2: DIFFERENTIATION PATHWAYS FOR DIFFERENT ADULT STEM CELLS

Types	Differentiation Pathways
Hematopoietic stem cells	Gives rise to various kinds of hemocytes which include erythrocytes, B cells and T cells, basophils, eosinophils, and other cells involved in innate immune response
Mesenchymal stem cells	Bone marrow derived stem cells (bone marrow stromal stem cells and skeletal stem cells) can produce many cells like bone cells (osteoblasts and osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and stromal cells that support the formation of blood
Neural stem cells	Gives rise to three major types of brain cells: nerve cells, and two other types of non-neural cells (astrocytes and oligodendrocytes)
Epithelial stem cells	Gives rise to different types of cells like Absorptive cells, Goblet cells, Paneth cells and Enteroendocrine cells in deep crypts in the lining of the digestive tract
Skin stem cells	Stem cells of the epidermis can produce keratinocytes which can move to the surface of the skin and form a protective layer. The follicular stem cells can produce both the hair follicle and the epidermis

Clinical Stem Cell Applications in the Treatment of Some Major Diseases:

Diabetes: Diabetes mellitus (DM) is a type of endocrine disorder that is characterized by a condition called hyperglycemia which results from varying levels of either insulin resistance or insulin deficiency [19, 20]. In diabetes, a patient's immune system leads to the destruction of insulin-producing β-cells in the pancreas [21] eventually leading to many complications.

Other forms of diabetes include diseases of the exocrine pancreas, endocrinopathies, and other infections. Diabetes has become a global health and economic concern and therefore demands challenging efforts toward successful solutions as the population suffering from diabetes has increased dramatically in the past few decades [22]. Scientists have been constantly working on finding ways to replace these insulin-producing cells. Pancreas and islet transplantation are some possible therapeutic approaches but the shortage of donors and evidence of a decline in β-cell function after transplantation restricts this treatment [23].

Stem cells have the potential to develop an abundant source of insulin-producing islet cells of the pancreas [24], and there are some encouraging results related to the treatment of this disease using ESCs. During the developmental phase of an embryo, the pancreas and liver arise from the same lineage which raises the interest to know if the liver cells can be developed into insulin-producing cells [25]. But there are studies suggesting that the microenvironment of a liver is not favorable because of its immunological, anatomical, and physiological factors that lead to the loss of islet mass after infusion. Theoretically, ESCs can be differentiated into any specific type of cell; pancreatic β-cells in this case, if given the required signals appropriately. But the potential advantage of using cells of this origin in the treatment of any disease is controversial because of many ethical issues. Many other different types of stem cell models are being used to successfully differentiate into β-cells in-vitro which include iPSCs, MSCs, and progenitor cells [22]. With the production of cells from various stem cell sources that produce insulin, their immunomodulatory properties along with self-renewal and differentiation capabilities make them a promising candidate to treat the complications related to diabetes [26] such as retinopathy, critical limb ischemia, diabetic nephropathy [27, 28] and even symptoms of diabetic neuropathy [29]. Some studies report that iPSCs have shown various limitations during clinical trials such as recurrent autoimmune attacks and potential tumor formation by the undifferentiated cells [30]. This is the reason why MSCs are being extensively studied by scientists investigating their feasibility in islet transplantation [31-33]. Encouraging studies resulting in the successful production of insulin-producing cells provide scope for treating diabetes using therapies based on stem cells.

Neurological Disorders: Loss of nerve cells in the brain or spinal cord causes neurodegenerative diseases which can be either acute or chronic in degeneration type. In acute degeneration, there is a localized loss of nerve cells at the site of injury, resulting in stroke or trauma. In chronic degeneration, generalized loss of neural population takes place and this has a chance of development over an extended period [34]. The timing of onset in such diseases remains unknown. The pathology of cell death and injury in such chronic neurodegenerative diseases is slow but the loss of a specific cell population continues. A brief list of a few chronic neurodegenerative diseases [35] and their pathological features are given in **Table 3.**

TABLE 3: LIST OF CHRONIC NEURODEGENERATIVE DISEASES AND THEIR PATHOLOGICAL FEATURES

Neurodegenerative Disease	Pathological Features
Parkinson's disease (PD)	Dopamine producing nerve cells die
Alzheimer's disease (AD)	Cells producing certain neurotransmitters die
Huntington's disease (HD)	Widespread loss of neurons
Amyotrophic Lateral Sclerosis (ALS)	Upper and lower motor neurons which activate different muscles die
Multiple Sclerosis (MS)	Cells which produce myelin responsible for the protection of nerve fibres are lost

Restoring lost cells can improve the impaired functions of the brain such as loss of memory and abnormal movement control, sensation, and other autonomic functions of our nervous system. Therapies based on stem cells are expected to give rise to new cells to repair and reconstruct the

circuitry of neurons and release the required neurotransmitters to improve the functions of the brain of an individual [35]. Several studies state the benefits of NSCs-based treatments for these chronic diseases [36-38]. Stimulation of NSCs and neurogenesis in-vivo after successful delivery of specific growth factors and cytokines in the damaged areas of the brain are some encouraging outcomes reported in a few studies [39]. In the past few decades, bone marrow-derived stem cells have been successfully used as neurorestorative tools to improve the recovery rate of an impaired brain. Even ESCs, FSCs / progenitor cells, UCSCs, and MSCs have been investigated for differentiation or transdifferentiation into functional nerve cells which can express specific markers of neurons, astrocytes, or oligodendrocytes *in-vitro* or *in-vivo*. Stem cell therapy is therefore an effective solution as it may have both neuroprotective as well as neurorestorative effects. But long-term safer and more effective studies are required during cell transplantation practices with the risk of tumorigenicity with systemic delivery of cells.

Parkinson's disease: Parkinson's disease (PD) develops due to the continuous deterioration of dopaminergic neurons in that section of the brain that functions in muscle movement control [40] *i.e.* substantia nigra [41]. The pathological hallmarks of PD include Lewy-body formation in pigmented neurons and neuritis, but its specific etiology is still under investigation [42].

Early in the disease, a dopamine precursor e.g. L-dopa or dopamine agonist [43] is supplied to the patients to increase dopamine levels and reduce the symptoms. This is the treatment option that is currently used, but its long-term efficiency is still uncertain [44]. The use of MSCs in mouse models suffering from PD significantly preserved the dopaminergic neurons [45, 46].

The use of NSCs has also been investigated for differentiation into functional dopaminergic-like neurons both *in-vivo* and *in-vitro*. This has been a major advancement in the treatment of PD and some studies report reduced symptoms of PD in an animal model after transplantation of NSCs[47]. Other studies encourage the use of iPSCs which when injected showed the activity of migration to various parts of the brain, differentiation into glia and neurons, and integration into the host brain with higher efficiency [48].

Alzheimer's disease: Alzheimer's disease (AD) is a disease because by neurodegeneration that is marked by cholinergic cell degeneration. AD is known for amyloid-β peptide plaques and neurofibrillary tangles [49] which lead to the death of many types of cells of neural lineage in different parts of the brain [50]. This results in cognitive impairment and memory loss and is therefore a most frequent form of dementia [51]. The progression of this disease results in extensive nerve cell losses well as synaptic contacts throughout the cortex, hippocampus, amygdala, and basal forebrain [52].

Nerve growth factor (NGF) can be a potential option for AD treatment but its transplantation into the brain using a cannula or its process to pass the brain-blood barrier has been unsuccessful in several reports. An effective way to diffuse NGF across the brain-blood barrier is to carry it using genetically modified cells. Stem cells are the best option available because of their higher migration capacity and higher mobility [53]. This will enable NGF to be distributed in larger amounts at a much faster rate [54]. Cellular therapies which enhance the growth of nerve cells or replacement of lost nerve cells can also help in delaying the development of AD [55]. This is an effective measure to maintain the count of cholinergic cells but requires further trials to validate the safety of this application.

Amyotrophic Lateral Sclerosis: Amyotrophic Lateral Sclerosis (ALS) is an adult-onset disease of neurodegeneration resulting from motor neurodegeneration in the cerebral cortex, brain stem, and spinal cord. It is also called Lou Gehrig's disease. ALS results in the death of upper and lower motor neurons leading to progressive paralysis [56].

NSCs can produce glial-restricted precursors (GRPs) and neuron-restricted precursors. Both of these can show differentiation into astrocytes, oligodendrocytes, or nerve cells. Some studies reported successful transplantation of lineage-restricted astrocyte precursors *i.e.* GRPs which showed survival abilities in the ALS animal model and also showed differentiation into astrocytes [57]. Some studies show that neurotrophic factors arising

after NSC transplantation increases neurogenesis and protects the nerve cells from ALS [58, 59]. These studies encourage the therapeutic strategy of cell transplantation to the cervical spinal cord to slow down the loss of focal motor neurons which is associated with ALS.

Multiple Sclerosis: Multiple Sclerosis (MS) is an autoimmune condition that develops because of the loss of glial cells that produce myelin *i.e.* oligodendrocytes. Oligodendrocytes progenitor cells derived from human ESC giving rise to oligodendrocytes have been observed in some studies which led to the remyelination of axons of the nerve cells restoring locomotion in animal models with spinal cord injury [60]. Some studies suggest successful oligodendrocytes replacement therapies using neural progenitor cells (NPCs) which reported enhanced remyelination capacity of the brain [61]. A study of transplantation of hESC-derived NPCs into the cerebral ventricles of an MS mouse model reported a reduction in the clinical signs of the disease and also showed neuroprotective effects [62]. Improvements in the function of the nervous system and slowing in the progression of the disease were observed after transplantation [63]. The use of HSCs to treat MS is under investigation, and it is expected to completely correct the anomalies of the immune system in a patient [64].

Huntington's disease: Huntington's disease (HD) is an autosomal dominant disease whose pathogenesis is still under investigation. HD leads to the involuntary activity of motor cells, the condition of dementia, and changes in personality and other cognitive impairments [34]. Treatment of HD using stem cells is an effective therapeutic strategy. Some studies report significant improvements in motor performance after the transplantation of NSCs into HD mouse models, also limiting degeneration of the neurons [65]. Neuroprotection and functional recovery were also reported in some studies after transplantation. But we still need to ensure the safety of the patient during the transport of NSCs to the pathological lesions which were caused because of the disease [66, 67].

Skin Aging: Skin is the outermost barrier that protects our body from losing excess water and also from infections from external microorganisms in the environment. It also has an important role in the appearance of an individual influencing their beauty in society [68]. The aging process starts from the day a child is born, and the skin of the human body shows obvious signs of it. There are many factors like air pollution, extended exposure to radiation from solar UV, poor nutrition, etc. which results in the thinning and drying of the skin, wrinkles, rough-textured appearance, and loss of elasticity [69,70]. This leads to structural and functional changes in the components of the extracellular matrix of cutaneous cells. Collagen, elastin, and proteoglycans function in providing tensile strength, elasticity, and hydration to the skin, but the process of aging slowly reduces the functions of these extracellular matrix components [70].

Antioxidants are being used as reducing agents as a solution for skin aging to some extent. Reactive oxygen species (ROS) play a crucial role in the changes to the components of the dermal extracellular matrix leading to aging. Antioxidants like Vitamin C and Vitamin E can prevent the activation of ROS by neutralizing them [71, 72].

But there are studies that suggest that overuse of antioxidant supplements like β-carotene, Vitamin A, and Vitamin E can harm us [73, 74] by eliminating all oxidants from our bodies [75]. The demerits of antioxidant treatment thus make transplantation of stem cells an encouraging option to treat the problem of skin aging.

So far, adipose-derived stem cells (ADSCs) have been studied to show improvement in the quality of skin as well as regeneration of skin during aging [66, 76]. There are studies suggesting that ADSCs can produce many growth factors like vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGFβ1 and TGFβ2) and many more which influences the surrounding dermal cells [46]. This seems to be a simple theoretical treatment, and encouraging outcomes have been marked in varying age groups, regardless of their biological background. Many studies and human trials have proven that stem cell therapy can reverse the effects of age-related problems safely

and productively thus providing humans with a cellular reboot to maintain the health of their bodies for longer [77].

Heart-related Diseases: Cardiovascular diseases (CVDs) affect the heart and blood vessels of a human 78 and have become a major cause of death across the globe [78, 79]. Heart dysfunction, death of cardiomyocytes, fibrosis, and scar tissue generation have been the major pathophysiological hallmarks of CVDs [80]. The most common among CVDs is hypertension which leads to an increased risk of stroke, myocardial infarction, and cardiac and renal failures [81]. The recuperative ability of the heart is not the same as the other organs and is limited to repair itself after injury [82], and the classical pharmacological treatments such as physical surgery and several other medicinal treatments have not been reported sufficient for the recovery of the injured cardiovascular tissue. The therapies which are currently available can only improve the symptoms and slow down the pathological progression of the disease, but they are unable to solve the problem of cardiac tissue repair [83].

Types of stem cells like ESCs, MSCs, and iPSCs have been reported beneficial in the application in regenerative medicine because of their pluripotent nature and the ability to self-renew. The administration of stem cells has also reported several beneficial effects like anti-inflammatory activities [84, 85], immunomodulation capacity [86] and other paracrine effects [87, 88]. Therapies based on stem cells can therefore be a promising therapeutic approach in treating CVDs and can help promote restoring the lost functions of the organ by repairing the injured tissues [78, 89].

ESCs possess the ability to directly differentiate into the cardiac lineage, but several concerns limit their applications. Among the limitations, ethical issues are of major concern in any research work using ESCs which prevents these cells from reaching their highest potential in clinical applications [90, 91]. MSCsto treats cardiac dysfunction has been possible because of its relatively easy process of isolation and expansion *ex-vivo*. MSCs can migrate to ischemic heart tissues [92] and can differentiate into spontaneously beating cardiomyocytes *in-vitro* after being treated with demethylating agent 5-azacytidine [93].

Having the potential of cardiac pyrogenicity, several studies have also reported improved functions of the left ventricle, reduction in the size of infarction, greater vascular density, and increased survivability chances after xenotransplantation of MSCs derived from the human bone marrow into murine models [94, 95]. Other advantages of MSCs in the repairing of damaged myocardium is their ability to suppress immune rejection and curb inflammatory responses as these cells lack major histocompatibility class II (MHC-II) antigens and possess the activity for down-regulation of host natural killer cells and T-cells [96]. The use of umbilical cord MSCs for the treatment of heart diseases has gained interest because of their non-invasive ease of extraction, high yield of MSC, and shorter doubling time. But their clinical trials are currently underway [97]. There is a microenvironment or niche (apex and atria) in a heart that plays a critical role in the maintenance of stem cells in an undifferentiated state, and during physiologic or pathological conditions, can give rise to cardiac progenitor cells.

These cells can migrate to the sites of myocardial injuries and can differentiate into the three major types of cells of the myocardium (cardiomyocytes, smooth muscles, and muscular endothelial cells) to repair the damage [78]. In a study, it was reported that these heart-derived cells outperformed MSCs derived from the bone marrow and adipose tissues in a preclinical animal model [98]. Thus, cardiac stem cells based therapies present an interesting option to treat patients having ischemic cardiac disease, hypertension, and myocardial infarction.

Using iPSCs is an exciting option whose applications are under extensive investigation, but these cells have certain limitations among which is the time required to extract the cells that possess specificity to the patients. Therefore, this treatment is not useful under urgent situations during acute myocardial infarction or rapidly progressive heart failure [82].

All these stem cell types can help in the production of functional and contractile heart muscle *in-vitro* and *in-vivo*, and the ability to release various soluble factors to stimulate endogenous cardiac stem cells, formation of new blood vessels, and other immunomodulatory effects positively

influence the functions of the heart as well as regeneration of myocardium to repair the injured tissue [89]. A large number of clinical trials have reported the safety and feasibility of many stem cell types, but a much better understanding still required on cardiac myogenesis to develop advanced stem cell therapeutics that can repair or regenerate the mutilated heart tissue to treat heart diseases [82, 89]. Heart transplantation is the last option for severe cardiac failure but the procedure is very difficult because of the limited availability of heart donors and other complications including the cost of transplantation. Therapy based on stem cells is therefore a potential future topic to overcome heart injuries [79].

Cancer: Treatment of cancer generally involves surgical resection, radiotherapy, and chemotherapy, but the efficacies of these therapeutic strategies are limited by the side effects related to the treatment, resistance to drugs, or other off-target effects. The ability of cancer cells to metastasize makes these therapies inefficient and therefore the chances of elimination of such cells get highly reduced leading to the recurrence of cancer. The properties of stem cells to migrate toward cancer cells, secrete various bioactive factors to promote anti-tumor effects, and their ability to immunosuppression promotes the targeting of tumors. Stem cell-based therapies have shown a promising trend in the treatment of cancer during the past few years. These cells have also proved their successful applications in regenerative medicine, immunotherapy, and cancer stem cell therapies targeting, and also in the screening of anticancer drugs.

On physical interaction with the tumor cells, stem cells can change the phenotypes of tumor cells with the help of their secreted bioactive factors and thus exert intrinsic anti-tumor effects [99]. Studies that provide the possible mechanisms of stem cell migration to malignant cells, and the release of bioactive molecules. Hypoxia triggers the transport of NSCs to the foci of the tumor which induces the activation of various chemoattractant expressions [100]. Interaction between chemokine CXCL12 and its receptor CXCR4 leads to the migration of directional HSCs[101]. Several chemokines and growth factor receptors which are expressed by MSCs are also involved in tumor targeting [102]. Factor 1 derived from a stromal cell, (SDF1)/CXCR4 axis also participates in helping other stem cells to migrate [103]. Controlled release of chemokines from biomaterials increases the stem cell recruitment towards the target. Therefore, stem cells are being manipulated with increased levels of chemokine receptors, or the target tissues are being engineered to secrete more bioactive molecules to improve the directed tumor targeting [104]. Having the properties of self-renewal and differentiation, stem cells such as HSCs have been widely used in repairing human tissues after the treatment of cancer using a high dose of radiotherapy or chemotherapy [105]. The patient-derived iPSC can be used to repair or regenerate the tissues which were damaged due to treatment [106, 107]. Cancer stem cells (CSCs) are known to attract normal stem cells which is the reason why normal stem cells are being engineered to target CSCs to ensure the high therapeutic efficacy of cancer therapy and also prevent the recurrence of the tumor [108].

In a cancer patient, stem cells can also play a role as in-situ drug factories and secrete various anti-tumor agents to overcome certain limitations of cancer therapies. TNF-α related apoptosis-inducing ligand (TRAIL) is a widely used secreted therapeutic agent which induces apoptosis of tumor cells [109]. Stem cells can also be engineered to selectively transport proteins that promote growth inhibition (e.g. IFN-β) and thus making the microenvironment unsuitable for the growth of the tumor.

Retinal Diseases: Diseases caused by degeneration of the retina develop due to the continuous loss of light-sensing photoreceptor cells which leads to a progressive decline in visibility [110]. To regenerate these photoreceptor cells in large numbers at an ideal developmental stage, limiting their potential to cause any malignancies and immunogenicity is a challenge in the treatment of degeneration of the retina [111]. Studies on stem cell transplantation promote a promising approach towards restoring visual functions in eyes and treatment of various diseases associated with degeneration such as retinitis pigmentosa (RP), Stargardts' dystrophy (STGD), and age-related macular degeneration (AMD). Therapies based on stem cells can help in generating new retinal cells and replace the damaged retinal cells with the new cells in a diseased retina [112].

As discussed earlier, stem cells possess the ability to differentiate into different cell types including retinal nerve cells and photoreceptor cells. Experimental studies report the successful promotion of cell regeneration after the administration of stem cells against diseased retinal cells. Studies have also reported new intercellular connections and improved visual functions [113]. Experiments using ESCs-derived RPE (retinal pigment epithelium) cells have reported similar morphology and essential functions of the native RPE cells. These RPE cells help in retinol cycling, nutrient transportation, and production of growth factors along with the phagocytosis of fragile photoreceptors [114]. Having similarities in morphological and functional properties with the native RPE cells make ESC a good source of cells to be used for transplantation. But this origin is ethically controversial and thus makes a way for experiments using other types of stem cells to treat various kinds of retinal degenerations [115].

Experimental studies related to iPSCs have reported improved retinal functions in rats when analyzed using electroretinogram (ERG) because of the differentiation of human iPSCs into RPE cells [116]. The expression of RPE cell markers in these iPSCs-derived RPE cells resulted in improved ERG responses in rats and was therefore considered as RPE-like cells in terms of both morphology and function, and risk-free in application because of no tumor formation after the experiments [117]. These iPSCs after derivation from patients must be corrected *ex-vivo* for any gene defects before reintroduction into the host for improved efficacies of the treatment [111]. Application of bone marrow-derived MSCs when injected into the subretinal space in rats with retinal degeneration showed repairing activity against the degenerating retina [118, 119]. Several studies also reported the prevention of light-induced retinal damage with the help of various factors that are secreted from hMSCs [120, 121]. These MSCs also reported differentiation into different types of retinal cells such as RPE-like cells, having similar morphological features and functions to promote the replacement of damaged cells of the retina without immunological rejection.

Teeth and Bone Related disorders: Teeth function in articulation, mastication, or aesthetics, and are difficult to recreate because of their complicated structure. But they have the benefit of being a natural and non-invasive source of stem cells [122]. Residing inside the dental pulp, dental pulp stem cells (DPSCs) can show differentiation into osteogenic and chondrogenic cells. The MSCs of the dental pulp has been reported to show differentiation into odontoblast-like cells and osteoblasts to form dentin and bone [123]. These DPSCs can produce all the structures of a developed tooth and are therefore an ideal source for dental tissue engineering because of their easy access to surgical procedures, ability to be stored under cryopreservation, production of dentin tissues in large amounts along with anti-inflammatory properties. Periodontal ligament stem cells (PDLSCs) can differentiate into mesenchymal cell lineages to give rise to cells forming collagen, adipocytes, cementum tissue, and osteoblast-like cells *in-vitro*, and therefore are being investigated to be used in the regeneration of periodontal ligament or cementum tissue [124].

Dental follicle stem cells can differentiate into cementoblasts, osteoblasts, and cells of the periodontal ligament [125], and are a promising source for the regeneration of teeth. The potential of dental stem cells to regenerate damaged dentin and pulp or to repair other perforations depend immensely on the regeneration of nerve and blood vessel networks. Bone marrow-derived MSCs have been reported to repair damaged bone and cartilage. Osteoarthritis (OA) is a pathological condition of joints when the protective cartilage that cushions the ends of bones wear down over time [126].

The avascular nature of the articular cartilage and its limited regenerative capacity leads to such conditions [127]. Osteonecrosis of the femoral hip (ONFH) is a refractory disease associated with the collapse of the femoral head which occurs due to poor blood supply [128]. A common treatment for the above two conditions is arthroplasty, but it is not recommended for younger patients because of its requirement for several surgical procedures in the future after the treatment. Stem cell-based therapy can provide a therapeutic approach to stop the onset of conditions like OA and ONFH [129], but the procedures are not well developed yet and will require further research for their long-term efficacy.

Studies reported improved quality in cartilage, and reduction in pain and disability after intra-articular injection of MSCs in patients suffering with OA [130]. Even experiments on patients with degenerative disc disease showed improvements in pain and disability, but without any recovery in height of the disc [131]. Use of MSCs in the field of regenerative orthopedics has shown beneficial results in the treatment of meniscus, intervertebral disc, ligaments, and tendon [132, 133], or muscle injuries [134]. But the ideal combinations of mechanisms to produce cells and bioactive factor administration must be well identified to meet the desired safety and efficacy of the treatment [135].

CONCLUSION: This review tried to address the basic knowledge of stem cell biology and its potential applications. Since knowledge of stem cell biology keeps on growing, we must carefully study their capacity to proliferate and differentiate uncontrollably for the most effective means to use these cells, from adult, fetal, neural, and embryonic sources, and activate their differentiation process in a controlled way for in vitro culture of tissue and for cell replacement therapy. Stem cell-based therapy is currently in use for the treatment of several diseases and conditions, and their impact on the upcoming medical sector seems to be promising. For stem cells to develop into a more patient-friendly and widely accessible therapy, the possibilities associated with the development of tumors after the administration of stem cells must be strictly assessed. Using a patient's cells to gain tolerance between the administered stem cells and the immune system of a patient's body is a challenging and promising study that is currently under extensive investigation.

Improving the efficiency of differentiation of stem cells will help in making the treatments based on stem cells more reliable and trustworthy. Continuous development in studies on stem cells is expected to even reduce the cost of treatments for various currently incurable diseases in the future. Thus stem cell therapies and its regenerative benefits have given us hope for the advancement of the future healthcare sector.

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