

**“STEM CELL THERAPY”-A REVIEW**

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**ABSTRACT**

The regeneration of a lost tissue is known to mankind for several years. The research on regenerative medicine has gained momentum in the field of molecular biology. Stem cells have been successfully isolated from variety of human tissues. Initial evidence from pioneering studies has documented that stem cells are used for various life-threatening diseases that have so far defeated modern medical care. The growing understanding of biological concepts in the regeneration of human tissues coupled with experiments on stem cells is likely to result in a paradigm shift in the therapeutic medicines. This review focuses on the origin of stem cells, their types, their properties, characteristics, their potential applications, therapies for various diseases and recent advances in the stem cell therapy.

**KEYWORDS:** Stem cell, pluripotent, self renewal, differentiation, stem cell therapy for diabetes, cancer, arthritis, Parkinson's and Alzheimer's disease.

**INTRODUCTION**

Stem cells are the body's natural reservoir – replenishing stocks of specialized cells that have been used up or damaged. Inside one's bone marrow, stem cells make 100,000 million new blood cells one needs every single day. Stem cells have the unique ability to produce both copies of themselves (self-renewal) and other more specialized cell types (differentiation) every time they divide. Stem cells, therefore, are essential to the maintenance of tissues such

as blood, skin, and gut that undergo continuous turnover (cell replacement), and muscle, which can be built up according to the body's needs and is often damaged during physical exertion. Stem cells are found in the early embryo, the foetus, placenta, umbilical cord, and in many different tissues of the body. Recently, stem cells have also been engineered from somatic cells. They are used in the treatment of many disorders and the research in the modification of the existing treatment of various genetic disorders is still going on.<sup>[1]</sup>

## **TYPES OF STEM CELLS**

Various types of stem cells are observed in the human body which are classified as.

**1)“TISSUE STEM CELLS”** - also sometimes called adult stem cells because each type of adult stem cell produces only a limited set of specialized cells characteristic of a particular tissue — epidermis, blood, and so on - are derived from or resident in a fetal or adult tissue. Usually they can only give rise to the cells of that tissue. In some tissues, these cells sustain turnover and repair throughout life. In adults, tissue-specific stem cells are located throughout the body. The so- called hematopoietic stem cells in bone marrow and umbilical cord blood, which make all the different types of blood cells, are the easiest to isolate, and have been used in therapy for decades as bone marrow transplants for diseases such as leukemia, where the normal development of blood cells has gone awry. For example, stem cells that are found in the skin will produce new skin cells, ensuring that old or damaged skin cells are replenished.<sup>[2]</sup>

**2)“EMBRYONIC STEM CELLS”**-These cells are derived from a small group of cells (called the inner cell mass) within the very early embryo. Human embryonic stem cells are obtained from embryos that are 5-6 days old. At the stage that embryonic stem cells are derived, the embryo is called blastocyst. Embryonic stem cells are said to be pluripotent – they are able to form all the different types of cell in the body, including germ cells.<sup>[2]</sup>

**3)“INDUCED PLURIPOTENT STEM CELLS”**- Recently, a third type of stem cell, with properties similar to embryonic stem cells, has emerged. Scientists have engineered these induced pluripotent stem cells (iPS cells) by manipulating the expression of certain genes - 'reprogramming' somatic cells back to a pluripotent state.<sup>[2]</sup>

## STEM CELL BANKING

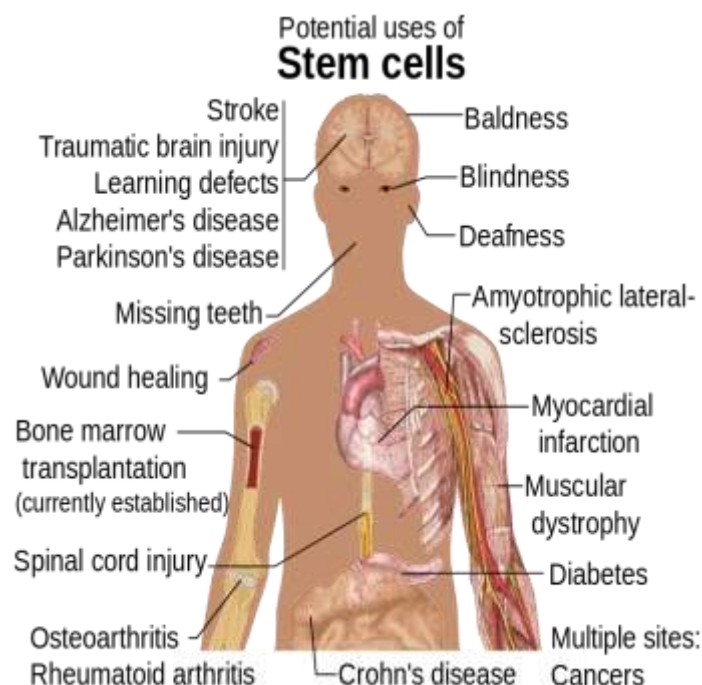
Stem cells which is obtained from cord blood can be preserved in the banks. Cord blood, which contains powerful life saving cells called stem cells, comes from a newborn's umbilical cord and is collected immediately after birth. Once the umbilical cord has been clamped and cut, the remaining blood in the umbilical cord is drawn into a collection bag. It may be then tested, frozen and subsequently stored in a cord blood bank for future use for the treatment of various diseases. Cord blood stem cells have been successfully used in transplant medicine for more than 20 years. Cord blood has been used to treat many life-threatening diseases including leukemia, other cancers, blood disorders, metabolic disorders, and immune diseases.<sup>[3]</sup>



## MEDICAL USES OF STEM CELL THERAPY

Disease and conditions where stem cell treatment is promising or emerging are:<sup>[4]</sup>

- Research
- Clinical trials
- Neurodegeneration
- Brain and spinal cord injury
- Blood cell formation
- Baldness
- Missing teeth
- Deafness
- Diabetes
- Transplantation
- Orthopaedics
- Infertility
- HIV/AIDS.



### STEM CELL BASED THERAPY

Adult stem cells have been used in pilot studies as potential cell-based therapy for various diseases. The following stem cell characteristics make them good candidates for cell-based therapy.

1. Potential to be harvested from patients.
2. High capacity of cell proliferation in culture.
3. Ease of manipulation to replace existing nonfunctional genes via gene splicing methods.
4. Ability to migrate to host target tissues (homing).
5. Ability to integrate into host tissues and interact with the surrounding tissues.<sup>[5]</sup>

### PROCESS OF STEM CELL BASED THERAPY

Stem cells derived from either peripheral blood, cord blood, bone marrow, or any adult tissue transported in the right medium to the laboratory is centrifuged, trypsinized, and propagated under ideal conditions and stored in the master cell bank (MCB). The MCB is further passaged to yield colonies of stem cells, given the right inductive signals using appropriate growth factors to allow them to differentiate into required cell types. These are injected or implanted into a patient as cell-based therapy. Homing will ensure that the stem cells reach the site of injury/tissues. Today, the two common methods of cell delivery are intravenous injection (direct delivery of cells) and cell encapsulation systems (indirect delivery of cells

using a carrier). The cell encapsulation approach uses a biocompatible, biodegradable material construct that is seeded with cells and implanted into defects in order to regenerate the lost tissue.[5]

### STEM CELL THERAPY FOR DIABETES

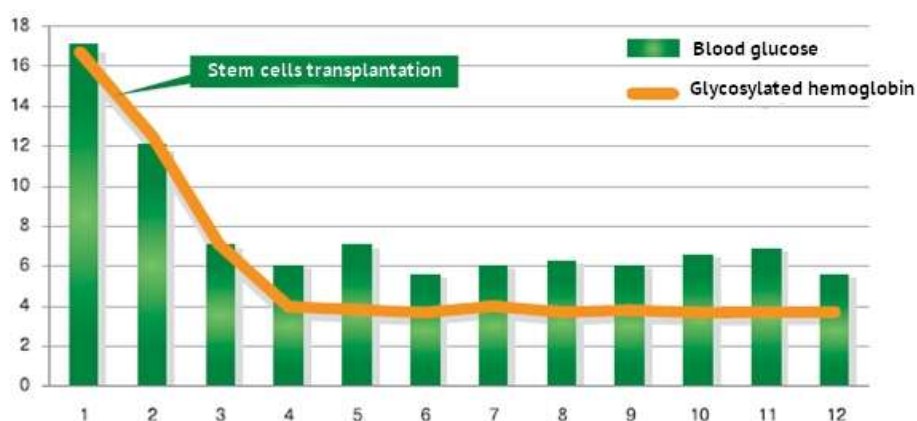
Diabetes mellitus (or diabetes) is a chronic, lifelong condition that affects your body's ability to use the energy found in food. There are three major types of diabetes: type 1 diabetes, type 2 diabetes, and gestational diabetes. Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic cells, with pancreas or islet-cell transplants[6].

Stem cell therapy for diabetes implies the replacement of diseased or lost cells from progeny of pluripotent or multipotent cells. Both embryonic stem cells (derived from the inner cell mass of a blastocyst) and adult stem cells (found in the postnatal organism) have been used to generate surrogate cells[6] or otherwise restore cell functioning. In isolated pancreatic tissue, pancreas-resident progenitor cells might give rise to endocrine islet cells.

Human and rodent pancreatic-duct cells[7,8], islet-derived cells[9,10], and exocrine tissue[11] contain cells that can differentiate towards a pancreatic endocrine phenotype. These tissues, cultured and differentiated in vitro, have been transplanted and can reverse diabetes mellitus in rodents. Rodent-liver stem cells and human fetal-liver cells have been differentiated in vitro into insulin-secreting cells by culture methods and/or introduction of cell-specific genes. When transplanted, these cells reverse diabetes mellitus in rodents[12]. Cells within liver that can differentiate into insulin-secreting cells after introduction of  $\beta$ -cell-specific genes have also been seen in vivo after adenoviral gene-delivery into rodents that have been rescued from diabetes for long periods[13,14].

A bone-fide pancreatic stem cell for cell regeneration remains elusive. A genetic-marking study in mice casts doubt on the existence of any cell progenitor cells and suggests that cells regenerate only by proliferation of existing cells[15]. In human beings, early immunological intervention to stop cell destruction during the development of type 1 diabetes mellitus allows recovery of pancreatic endocrine function[16,17]. This finding might in part be attributable to recovery in cell mass by recruitment of local pancreatic or extrapancreatic progenitor cells that differentiate into cells and/or proliferation of remaining cells during protection from immune-mediated destruction.

Dynamics of glucose and glycosylated hemoglobin content in blood plasma after transplantation of hemapoietic stem cells



### STEM CELL THERAPY FOR COLLAGEN INDUCED ARTHRITIS (CIA)

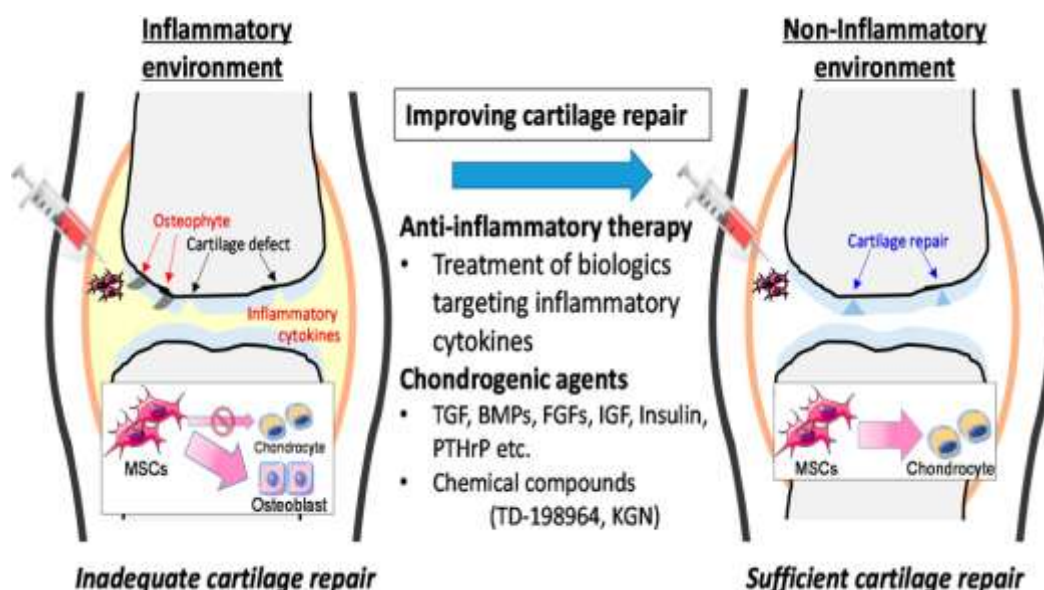
Collagen-induced arthritis (CIA) is an animal model of rheumatoid arthritis (RA) that is widely used to address questions of disease pathogenesis and to validate therapeutic targets. Arthritis is normally induced in mice or rats by immunization with autologous or heterologous type II collagen in adjuvant.

Mesenchymal stem cells (MSCs) are precursors of tissue of mesenchymal origin, but they also have the capacity to regulate the immune response by suppressing T and B lymphocyte proliferation in a non-major histocompatibility complex-restricted manner.

The heterogeneity of the MSC population is reflected by the absence of a unique, specific molecular marker. MSCs derived from different tissues express developmental markers of mesenchymal, endothelial, and hematopoietic tissues.<sup>[18-20]</sup> but they also produce molecules directly involved in regulation of the immune response, such as the costimulatory molecule CD28, the inhibitory molecules programmed death ligand 1(PDL-1) and PDL-2 and an array of different cytokines<sup>[21,22]</sup>. Through these molecules, MSCs can regulate the immune response.

A single intraperitoneal injection of allogeneic MSCs given at the moment of immunization with CII was sufficient to prevent the occurrence of bone and cartilage erosions in the joints of immunized mice. These are permanent, irreversible lesions corresponding to the recent characterization of MSCs and their role in hematopoiesis and immune modulation suggests their potential use for cell therapy most severe grade of disease and are never observed in MSC-treated mice. The use of MSCs for cell therapy greatly relies on their capacity to

engraft and survive long-term in the appropriate target organs<sup>[23]</sup>, contributing to the repair of injured tissues.<sup>[24,25]</sup> Their plasticity and capacity to undergo orthodox and unorthodox differentiation processes allowed the use of MSCs, alone or combined with biomaterials, for repair of tissues, such as bone<sup>[26]</sup>, heart<sup>[27,28]</sup>, kidney<sup>[29]</sup>, lung<sup>[30,31]</sup>, and brain.<sup>[32]</sup> However, in the experiments it was found that MSC viability was not required for their long-term immunosuppressant action; MSCs were, in fact, detectable in the recipient for no more than 10 days after treatment. During this time lag, they were able to “educate” other cells to inhibit the pathogenic immune reaction. Current therapy for RA is directed toward diminishing the inflammatory response and treating the uncontrolled inflammation. To date, it has not been possible to prevent the disease or to completely arrest the disease process through medical therapy. However the research results represent an effective new therapeutic approach to target the pathogenic mechanism of autoimmune arthritis using adult stem cells.<sup>[33]</sup>

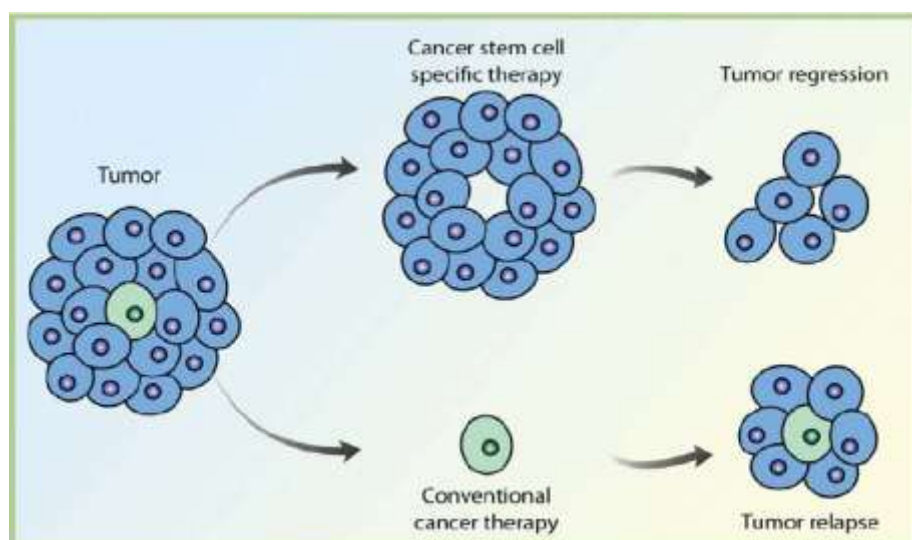


## STEM CELL THERAPY FOR CANCER

Cancer, also known as a malignant tumor or malignant neoplasm, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.

Numerous studies have indicated that several human cancer types, including those of the blood, brain, skin, lung, kidneys, gastrointestinal tract, pancreas, liver, ovarian, prostate and testis cancers, might arise from the malignant transformation of stem cells and their progenitors into cancer progenitor cells<sup>[34-44]</sup>. Several *in vitro* and *in vivo* studies have been carried out with a variety of cancer cell line types and on different animal models to identify

new therapeutic targets to block the growth and/or survival of the cancer cells. Among them, the molecular targeting of distinct oncogenic signaling elements, which are activated in the cancer cells during the progression of numerous cancer, represents a promising strategy for the development of new chemopreventive treatments and combination therapies against some aggressive and metastatic cancers. The aberrant expression and/or activity of diverse hormones, growth factors, cytokines and chemokines (androgens, estrogens, EGF and TGF- $\alpha$ /EGFR, IGF/IGFR, SHH/SMO, Wnt/ $\beta$ -catenin, Notch, TGF- $\beta$  and SDF-1/CXCR4) and tumorigenic signaling elements (telomerase, PI3K/Akt, NF- $\kappa$ B and Myc-1) may contribute to the sustained growth and survival of stem cells as well as their malignant transformation during the initiation and cancer progression<sup>[45-50]</sup>. Therefore, their molecular targeting is of importance to eliminate cancer progenitor cells, and thereby inducing a complete tumor regression and cancer remission.

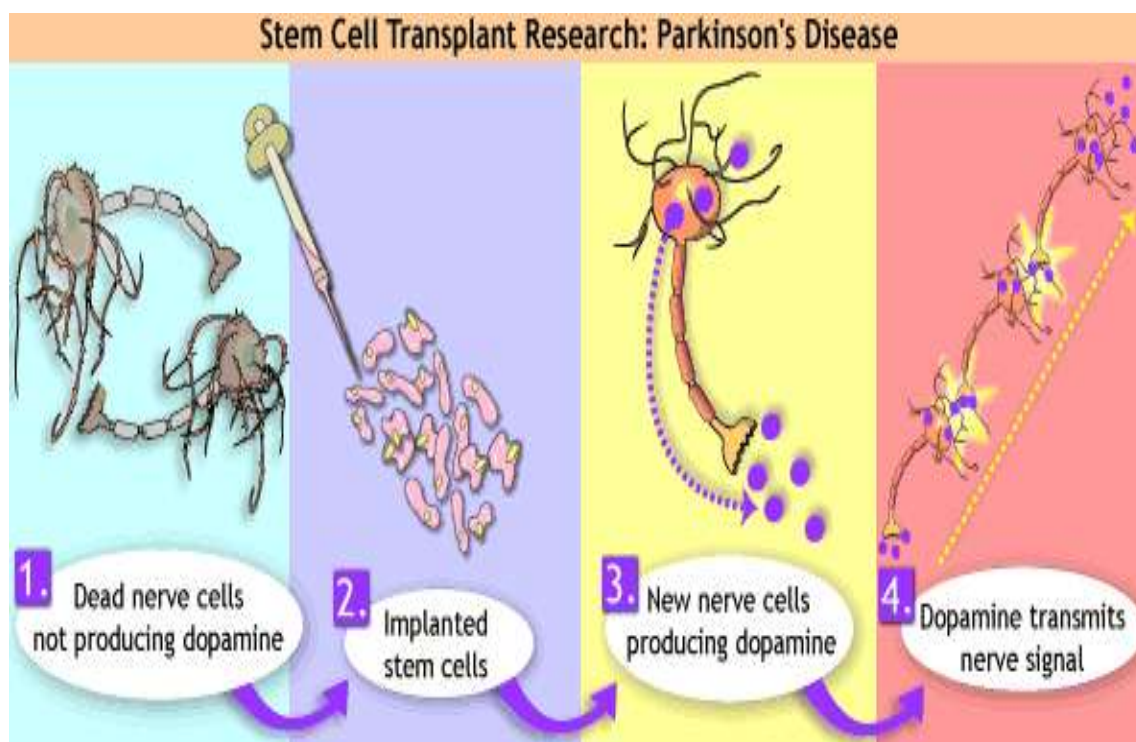


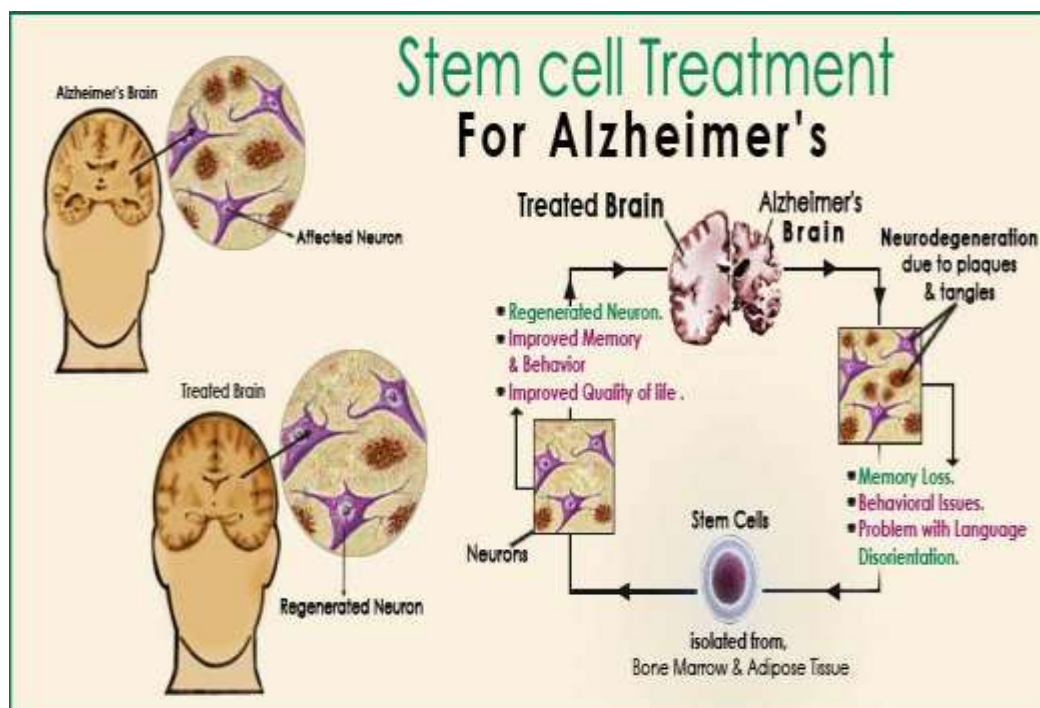
### STEM CELL THERAPY FOR PARKINSON'S AND ALZHEIMER'S DISEASE

Parkinson's disease affects the nerve cells in the brain that produce dopamine. Parkinson's disease symptoms include muscle rigidity, tremors, and changes in speech and gait. Alzheimer's disease (AD), also known as Alzheimer disease, or just Alzheimer's, accounts for 60% to 70% of cases of dementia. It is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. The most common early symptom is difficulty in remembering recent events (short-term memory loss). As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues.

The motor dysfunctions which are associated with Parkinson's disease result from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, a region of brain that controls muscle movement. Therefore, cell replacement therapy by delivering new dopaminergic neurons represents a putative strategy for the treatment of this neurodegenerative disease<sup>[51-53]</sup>.

A high yield of differentiation of the mouse and human ESCs into the midbrain TH+-dopaminergic neurons has been obtained *in vitro* in a stromal cell-derived inducing activity (SDIA) system or by co-culture with PA6 cells. Importantly, these neuron-like cells expressed the specific markers of dopaminergic neurons, including the dopamine transporter, aromatic amino acid decarboxylase, and the transcription factors associated with neuronal and dopaminergic differentiation (Sox1, Nurr1, Ptx3 and Lmx1b). These cells were also transplantable and a small number survived in the 6-hydroxydopamine (6-OHDA)-treated mouse or rat striatum. In addition, Alzheimer's disease which is characterized by regional neuronal degeneration and synaptic loss and associated with the presence of senile plaques, also represents a degenerative disorder that could benefit from neural cell delivery in the brain.<sup>[54]</sup>





## CONCLUSION

Stem cells derived from all sources hold immense medical promises. Stem cell therapies have virtually unlimited medical applications. While there are several barriers that need to be broken down before this novel therapy can be translated from lab to clinics, it is certain that the future is going to be exciting for all of us. We have moved on from the surgical model of care to the medical model and are likely to move onto the biological model of care. The need of the hour is high-quality research coupled with collaboration between basic scientists and the clinicians for the advancement and newer approaches for this therapy. Recent developments in the technique of stem cell isolation and expansion together with advances in growth factor biology have set a stage for successful stem cell therapy. Stem cell therapy has proved beneficial for genetic as well as induced disorders and find its application for treating many diseases. Stem cell therapy has brought in a lot of optimistic hope amongst researchers, doctors, and the patients who are the chief beneficiary of this innovation.

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