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REVIEW ON: STEAM CELL THERAPY

Priyanka Panmand*, Suraj Pabale, Anuradha Panchal, Siddheshwar Naykode, Aishwarya Koli, Shravani Yewale

Department of Pharmaceutics, K.B. Institute of Pharmaceutical Education and Research, Pune, Maharashtra, India.

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***Corresponding Author: Priyanka Panmand**
Department of Pharmaceutics, K.B. Institute of Pharmaceutical Education and Research, Pune, Maharashtra, India.
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ABSTRACT

Because they are unspecialized cells with the ability to replicate asymmetrically over and over, stem cells have distinctive qualities. Different types of stem cells exist, and they are distinguished by their potency and/or uniqueness. A newer method of treating a number of disorders is cell therapy. The potential of stem cells to restore failing tissues and organs has sparked intense curiosity, as it seemed like the only practical therapeutic approach. This review paper sought to clarify the many sources of stem cells and their therapeutic uses since they appear to be a potent tool for regenerative medicine in the future.

KEYWORDS: Stem cell; Classifications; Differentiation; Clinical applications.

INTRODUCTION

Stem cells, you've heard about stem cells in the news, and perhaps you've wondered if they might help you or a loved one with a serious disease. Here are some answers to frequently asked questions about stem cells.

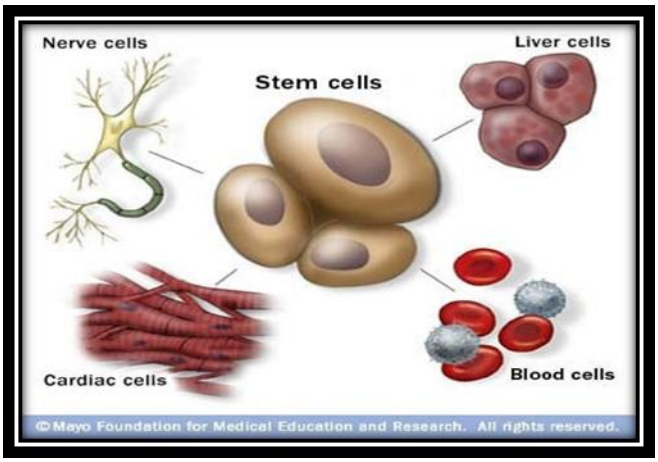

Figure No. 1: Stem cells: The body's master cells.

Stem cells are a special type of cells that have two important properties. They are able to make more cells like themselves. That is, they self-renew. And they can become other cells that do different things in a process known as

differentiation. Stem cells are found in almost all tissues of the body. And they are needed for the maintenance of tissue as well as for repair after injury.

Depending on where the stem cells are, they can develop into different tissues. For example, hematopoietic stem cells reside in the bone marrow and can produce all the cells that function in the blood. Stem cells also can become brain cells, heart muscle cells, bone cells or other cell types.

No other cell in the body has the natural ability to generate new cell types.

History

- ✓ 1998 saw the publication of two papers describing the growth *in vitro* of human embryonic stem (ES) cells derived either from the inner cell mass (ICM) of the early blastocyst or the primitive gonadal regions of early aborted fetuses. Work on murine ES cells over many years had already established the amazing flexibility of ES cells, essentially able to differentiate into almost all cells that arise from the three germ layers.[2]
- ✓ STEM was initiated in 1990s by National Science Foundation in the United States. Stem is a learning alternative to build 21st century ability and skills and face the challenges in industry.[1]
- ✓ Stem cell biology has attracted tremendous interest recently. It is hoped that it will play a major role in the treatment of a number of incurable diseases via transplantation therapy. Several varieties of stem cells have been isolated and identified in vivo and in vitro. Very broadly they comprise of two major classes: embryonic/fetal stem cells and adult stem cells. Some scientists wish to pursue research on embryonic/fetal stem cells because of their versatility and pluripotentiality, while others prefer to pursue research on adult stem cells because of the controversial ethical sensitivities behind embryonic/fetal stem cells. However, both embryonic/fetal and adult stem cells are equally important and research on both types must be enthusiastically pursued since the final objective is the application of this technology for the treatment of a variety of diseases that plague mankind. It is very possible that the findings from one stem cell type may complement that of the other.[3,4]
- ✓ The general designation, “stem cell” encompasses many distinct cell types. Commonly, the modifiers, “embryonic,” and “adult” are used to distinguish stem cells by the developmental stage of the animal from which they come, but these terms are becoming insufficient as new research has discovered how to turn fully differentiated adult cells back into embryonic stem cells and, conversely, adult stem cells, more correctly termed “somatic” stem cells meaning “from the body”, are found in the fetus, placenta, umbilical cord blood and infants.[2] Therefore, this review will sort stem cells into two categories based on their biologic properties - pluripotent stem cells and multipotent stem cells.[2]

Selection of Stem Cells

1. The capacity of differentiation: Embryonic stem cells can become all cell types of the body. Adult stem cells are limited to differentiating into the cell types of their tissue of origin.[2]
2. Grow in culture: Embryonic stem cells can be grown relatively easily in culture. Adult stem cells are rare in mature tissues, so isolating these cells from an adult tissue is challenging.[6,7]
3. ES cells, injected directly into another body, ES cells will differentiate into many different types of cells, causing a teratoma.[6]
4. Immune rejection: Identical matches between donor and recipient must be made for successful transplantation treatments, but matches are uncommon.[6]

5. Ethical considerations: many nations currently have limitations on either human ES cell research or the production of new human ES cell lines. The use of adult stem cells does not require the destruction of an embryo.[7]

Stem cells can help to:[53,57,58,59]

1. Increase understanding of how diseases occur. By watching stem cells mature into cells in bones, heart muscle, nerves, and other organs and tissue, researchers may better understand how diseases and conditions develop.
2. Generate healthy cells to replace cells affected by disease (regenerative medicine). Stem cells can be guided into becoming specific cells that can be used in people to regenerate and repair tissues that have been damaged or affected by disease.
3. People who might benefit from stem cell therapies include those with leukemia, Hodgkin disease, non-Hodgkin lymphoma and some solid tumor cancers. Stem cell therapies also might benefit people who have aplastic anemia, immunodeficiencies and inherited conditions of metabolism.
4. Stem cells are being studied to treat type 1 diabetes, Parkinson's disease, amyotrophic lateral sclerosis, heart failure, osteoarthritis and other conditions.
5. Stem cells may have the potential to be grown to become new tissue for use in transplant and regenerative medicine. Researchers continue to advance the knowledge on stem cells and their applications in transplant and regenerative medicine.
6. Test new drugs for safety and effectiveness. Before giving drugs in development to people, researchers can use some types of stem cells to test the drugs for safety and quality. This type of testing may help assess drugs in development for toxicity to the heart.
7. New areas of study include the effectiveness of using human stem cells that have been programmed into tissue-specific cells to test new drugs.
8. For the testing of new drugs to be accurate, the cells must be programmed to acquire properties of the type of cells targeted by the drug. Techniques to program cells into specific cells are under study.

How stem cell therapy Work

- ✓ It is also known as regenerative medicine, promotes the repair response of diseased, dysfunctional or injured tissue using stem cells or their derivatives. It is the next chapter in organ transplantation and uses cells instead of donor organs, which are limited in supply.[8]
- ✓ Researchers grow stem cells in a lab. These stem cells are manipulated to specialize into specific types of cells, such as heart muscle cells, blood cells or nerve cells.[9]
- ✓ The specialized cells can then be implanted into a person. For example, if the person has heart disease, the cells could be injected into the heart muscle. The healthy transplanted heart muscle cells could then contribute to repairing the injured heart muscle.[10]
- ✓ Researchers have already shown that adult bone marrow cells guided to become heart-like cells can repair heart tissue in people, and more research is ongoing.[11]

Potential problems with using embryonic stem cells in humans

1. For embryonic stem cells to be useful, researchers must be certain that the stem cells will differentiate into the specific cell types desired.

2. Researchers have discovered ways to direct stem cells to become specific types of cells, such as directing embryonic stem cells to become heart cells. Research is ongoing in this area.
3. Embryonic stem cells also can grow irregularly or specialize in different cell types spontaneously. Researchers are studying how to control the growth and development of embryonic stem cells.
4. Embryonic stem cells also might trigger an immune response in which the recipient's body attacks the stem cells as foreign invaders, or the stem cells might simply fail to function as expected, with unknown consequences. Researchers continue to study how to avoid these possible complications.

Sources of Stem cell

A. Autologous[8]

Extraction and storage of stem cells from patient (bone marrow or adipose tissue)

Lower risk of infection/rejection

Source of Stem Cells: Antilogous

1. Mobilization
2. Collection of stem cells
3. Procession: to purify and concentrate the stem cells; or culture cells to reprogram to stem cells
4. Cryopreservation
5. Chemotherapy
6. Reinfusion

Stem cells are collected from patient[9]

I. Mobilization of stem cells: patient will receive injections of a medication that makes an increase in production of stem cells.
II. Stem cells are collected from patient. Several harvesting procedures (between one and five) are usually needed to get enough stem cells.
III. The patient will undergo high doses of chemotherapy or a combination of chemotherapy and radiation therapy to kill the cancer cells and to get rid of the stem cells that are left in bone marrow.
IV. Reinfusion stem cells back to patient. This process is similar to having a blood transfusion. Now these bone marrow stem cells can make new blood cells.

B. Allogenic[10]

- ❖ Donor with matching tissue type
- ❖ Immune system suppression therapy
- ❖ Source of Stem Cells - Allogenic

1. Collecting stem cells from donor (bone marrow or blood)
2. Processing: to purify and concentrate the stem cells; or reprogram these cells
3. Cryopreservation
4. Patient treatment
5. Reinfusion

Stem cells are collection[11]

I. Stem cells are collected from donor's bone marrow or bloodstream.

II. Several harvesting procedures (between one and five) are usuallyneeded to get enough stem cells.

III. The patient will undergo high doses of chemotherapy or acombination of chemotherapy and radiation therapy to kill thecancer cells and get rid of the stem cells that are left in bonemarrow.

IV. Stem cells collected will be infused to patient. Meanwhile, thepatient will be treated with immune regulators.

Clinic Sources of Stem Cell Therapy

Sr. no.	Cell type	Origin
1.	Bone marrow derived stem cell	Bone marrow
2.	Skeletal myoblast	Adult skeletal muscle
3.	Cardiomyocyte progenitor cell/Cardiac stem cell	Adult or fetal heart
4.	Endothelial progenitor cell/endothelial precursor cell	Bone marrow/peripheral blood
5.	Embryonic stem cell	Blastocyst stage embryos
6.	Induced pluripotent stem cell	Any somatic cell

Types of Steam Cell

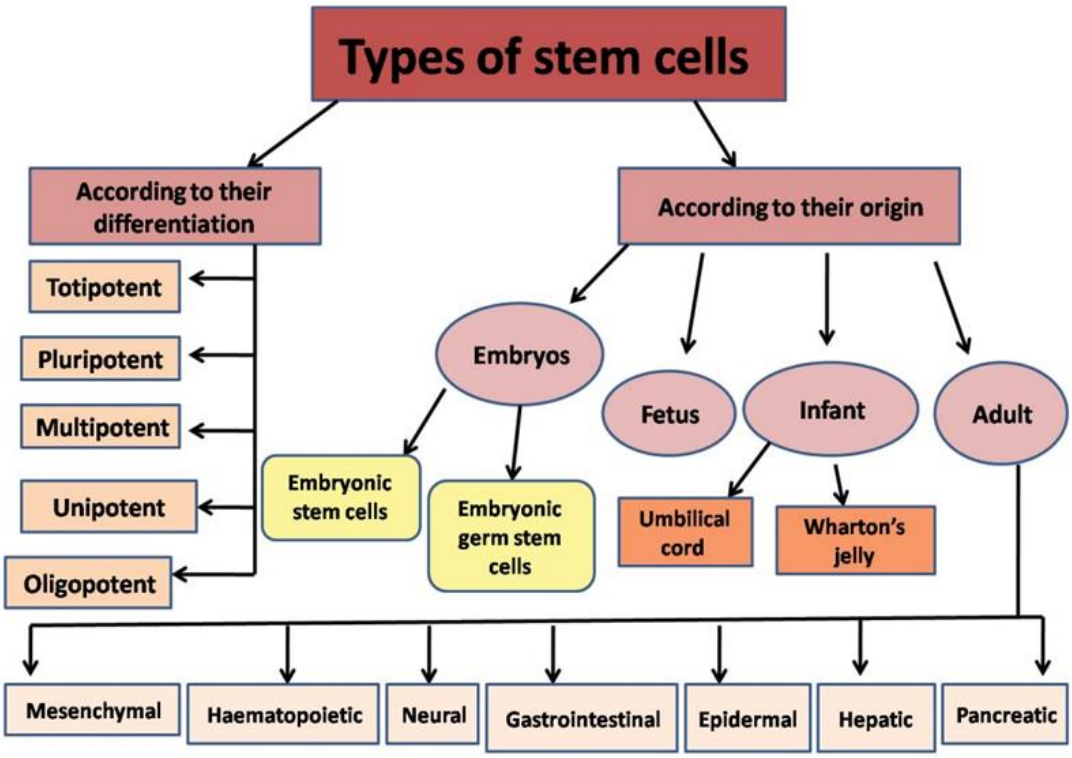

Figure No.2: Types of Steam Cell.

1. Stem cells classification according to their origin

A. Embryonic Stem Cells (ESCs)

Embryonic stem cells: Embryonic stem cells are pluripotent, self-renewing cells that can be derived from both mouse or human blastocysts, they are taken from the very early stages of embryo development after 4-5 days after fertilization. They can be stored in culture as undifferentiated cell lines and can be stimulated to differentiate into any cell line.[14] They can differentiate into endoderm, mesoderm, and ectoderm embryonic germ layers, and also any type of somatic cells. They, therefore, hold a great capacity in tissue regeneration therapy.[15]

a. **Embryonic Germ Stem Cells:** Embryonic Germ(EG) cells are taken from the later stages of the embryo development cells. They are derived from Primordial Germ line Cells (PGCs) in the early development. They are mainly isolated from the fetal tissue in narrow-window timing.[16] The PGC-derived cells were pluripotent, although, it was not possible to demonstrate pluripotency by generating the formation of teratomas in mice.[17]
b. **Fetal stem cells:** Fetal stem cells are primal cell types found in the organs of the fetuses. They are able to differentiate into two types of stem cells: pluripotent stem cells and hematopoietic stem cells. Neural crest stem cells, fetal hematopoietic stem cells and pancreatic is let cells have been isolated in the fetuses.[18] Human fetal stem cells have been used by many people, children and adults that are suffering from many of mankind's most devastating diseases.[19]

B. Infant stem cell

a. **Umbilical cord stem cells:** Umbilical cord blood contains prevalent stem cells which differ from those of bone marrow and adult peripheral blood.[20] Cord blood stem cells have shown to be multipotent as it being able to differentiate into neurons and liver cells.[20]
b. **Wharton's jelly:** Wharton's jelly, which is the umbilical cord matrix, is considering edtobea source of mesenchymal stem cells. These cells express typical stem cell markers, can be propagated for long times and can be induced to differentiate in vitro into neurons.[21]

C. Adult stem cell

Adult stem cells are any stem cells taken from mature tissue; they are found in the tissues of a fully developed child (whole embryo) or adult and can only produce a limited number of cell types. They have limited potential as compared to the stem cells that derived from embryos and fetuses because of the stage of development of these cells.[22] They play a vital role in tissue repair, regeneration; and they are referred to their tissue origin.[23] Bone marrow is an abundant source of adult stem cells.[24]

a. **Mesen chymal stem cells**: Mesenchymal Stem Cells (MSCs) area different population of cells with the potential to differentiate into various somatic lineages. They were at first described as adherent cells with a fibro blast-like appearance that can differentiate into osteocytes, chondrocytes, adipocytes, tenocytes and myocytes.[25]
MSC can be isolated from the bone marrow and readily discrete from the hemato poietic stem cells due to their plastic adherence.[26] They are used in tissue engineering and regenerative medicine.[27] They are character by long-storage without major loss of their potency.[28]
b. **Hematopoietic stem cells:** Hematopoietic stem cells are cells having the self-renewing potential and the capacity to give rise to differentiated cells of all hematopoietic lineages. Therefore, they transplanted for complete healing of hematologic disorders and after high-dose chemotherapy against malignant diseases.[29]
c. **Neural Stem Cells**: Neural stem cells are multi potent and self-replication cells; they are established in specialized molecular micro environments in the adult mammalian brain. They can display the potential role in cellular therapy of the brain.[30]
d. **Gastrointestinal stem cells:** The stem cells of the gastrointestinal tract residein a "niche" in the intestinal crypts and gastric glands. The mechanism and the direction of the diffusion of this converted clone in the gastrointestinal mucosa are hotly disputed, and the central to this case is the position and nature of the gastrointestinal stem cells.[31]
e. **Epidermal stem cells:** The mammalian epidermis is a rapidly rejuvenating tissue that consists of three types of

keratinocytes with varying differentiation potential: epidermal stem cells, Transiently Amplified Cells (TA cells) and terminally differentiated cells. The epidermal stem cells have free self-renewal power. They are establishing in the basal layer and remarkable in maintaining homeostasis and cellular regeneration of normal skin; wound healing and neoplasm formation, where as TA cells ,progeny of the epidermal stem cells, undergo terminal differentiation after 3–5 divisions. After division, TA cells leave the basal layer and move through the supra basal layers to the tissue surface, where they are periodically shed as squames.[32]

f. **Hepatic stem cells:** The liver has a strong regenerative capacity, utilizing different modes of regeneration according to the type and extent of the injury. Mature liver cells can propagate to replace the damaged tissue permit the recovery of the parenchymal function.[33] Chronic liver injury gives rise to a potential stem cell compartment which is located in the smallest branches of the intra hepatic biliary tree being activated, which called oval cell ductular reaction. These oval cells are derived from the canal of Hering, which amplifies this biliary populations prior to these cells differentiate into hepatocytes. In the human liver, the organization of the biliary tree is different, with the canal of hiring extending to the proximate third of the lobule and so apparently requiring a name change from oval cells to hepatic progenitor cells.[34]

g. **Pancreatic stem cells:** Insulin-producing cells previously generated from pluripotent stem cells. The generation of these cells would provide a novel cell source for drug discovery and cell transplantation therapy in people suffering from diabetes.[35] Insulin-producing beta-cells turnover every 40-50 days by processes of apoptosis and the propagation and differentiation of the newly islet cells from progenitor epithelial cells, which are located in the pancreatic ducts.[36]

Types of stem cells according to their differentiation

Stem cells can be classified according to their differentiation potential as a totipotent, pluripotent, multipotent, unipotent and oligopotent **(Figure2)**.

a. **Totipotent stem cells:** Totipotency means that it has the total potential to give rise to all types of cells. Totipotent is the capacity of a single cell to divide and differentiate into all cell types in an organism and produce fertile offspring. Oocytes and sperm are the best differentiated cells in our body and they are capable of forming any tissue in the body.[37]

b. **Pluripotent stem cells**: Pluripotency is the ability of the cells to produce any type of cells in the organism. They have been derived from the mouse embryo. All are capable of differentiating into cells representative of a variety of adult tissue types in various assays, including embryoid body, teratoma, and some can contribute to mouse development in chimeras. There are many differences being recognized among pluripotent stem cell types, such as their morphology, gene expression profiles and growth factor requirements.[38]

c. **Multi potent stem cells***:* Multi potency means to those cells that can only give rise to cells of the tissue from which they are isolated.[39]

d. **Uni potent stem cell**: Adult stem cells are found in the tissues of the adults they produce a limited number of cell types and can repair damaged tissue by replacing specialized cells. Because of the restricted lineage, they were thought to be either multipotent, with the ability to differentiate into a limited range of cells or unipotent, with the ability to produce only one cell type.[40]

e. **Oligo potent stem cells**: Oligo potency means to those cells that can differentiate into only a few cell types, like lymphoid or myeloid stem cells.[41]

Applications of Stem cells

1. Stem Cells and diabetes mellitus

Stem cells have generated incredible interest for repairing failing tissues and organs[52] (Table 2). Stem cell therapy has become at analyzing idea to provide glucose-responsive insulin-producing cells to Type 1 diabetic patients as an alternative to islet transplantation.[53] Mesenchymal stem cells will grow and differentiate according to their environment. When MSCs injected into the pancreas in vivo, it is expected that MSCs will differentiate into pancreatic cells that have both exocrine and endocrine functions. Thus, transplantation of MSCs from bone marrow stem cells can repair the pancreas in its role to provide para crine effects and other cell differentiation effects.[54]

A beneficial effect of MSC transplantation on diabetes via a direct effect of differentiation to cells capable of producing insulin, organ indirect effect of secretion of immune modulators, which prevent endogenous T cells from eliciting pancreatic β-cell destruction, or other as yet unknown factors, which influence insulin secretion reaction.[55]

2. Stem cell therapy and Parkinson's disease

Parkinson's disease (PD) is a wide spread neurodegenerative disease that characterized by bradykinesia, rigidity, and tremor. The pathological causes of PD are due to the Decrease of Nigro striatal Dopamine (DA) neurons, but neuronal degeneration also occurs in non-DA-ergic systems.[56] MSCs are capable of differentiating into tyrosine hydroxylase-positive neurons and can ameliorate motor performance in mice Parkinson's disease model.[57] Moreover, it has been demonstrated that cells with DA-ergic can be produced from both rat and human MSCs, and that transplantation of these cells showed an improvement of motor function in an animal model of PD.[58]

3. Stem cells and heart disease

Physicians of cardiac disease looking forward a remedy for the patients who are suffering from the heart disease. Cardiac transfer of stem and progenitor cells can have an adequate effect on tissue perfusion and contractile performance of the injure dheart.Stem cells have the potency to promote myocardial perfusion and contractile performance in patients who are suffering from acute myocardial infarction, advanced coronary artery disease, and chronic heart failure.[59]

4. Auto immune diseases

Autoimmune diseases are produced as a result of an immune response of the body versus the normal cells and tissues. According to their ability to modulate immune responses, MSCs have also been proposed as a treatment for autoimmune diseases. Patients who are suffering from severe autoimmune diseases do not respond to the standard therapy and often require autologous or allogeneic Hematopoietic Stem Cell Transplantation (HSCT).[60]

5. Liver diseases

Liver failure and cirrhosis occur as a result of a variety of chronic hepatic injuries. MSC s have the potential to be used for the treatment of liver diseases due to their regenerative potential and immune modulator properties. They display sequential and overlapping severe pathogenic processes that include severe inflammation, hepatocyte necrosis, and fibrosis/cirrhosis, and carry a high mortality rate.[64]

Table 2: Clinical applications of stem cells.

Source	Dosage	Disease	Route of administration	Conclusion
Bone marrow mesenchymal stem cells Insulin producing cells (IPCS)	$1x10^5$ MSCs cell/rat$1x10^5$ IPCs cell /rat	Diabetes mellitus Type I, Wistar rats	Tailve in injection	Stem cells, which can differentiate into IPCs, would provide a potentially free source of islet cells for transplantation and mitigate the major limitations of availability and allogeneic rejection. Therefore the use of stem cells is becoming the most favorable therapy for DM.[52]
Human umbilical cord blood-MSC (UCB-MSC)	-	APP and presenilin (PS1) double-trans genicmice	Hippocampus	Improved spatial learning and memory in Morris Water Maze tests Reduced A β load and tau hyper phosphorylation, inhibited pro inflammatory cytokine release from microglia.[66]
Bone marrow derived MSCs	$1x10^6$ cells perrat	Cirrhoticrats	Intravenous infusion at the tail vein	The exploration of the therapeutic potential of mesenchymal stem cells on hepatic cirrhosis will benefit millions of people who suffer from the end-stage of chronic liver diseases.[67]
Bone marrow MSCs	1.75×10^5	The sterile testes in Wistar male rats Erectile Dysfunction India beticrats	Injected in to the left testis	Testis of host infertile rats accepted transplanted MSCs. The transplanted MSCs could differentiate into germinal cells in testicular semen ferrous tubules.[68] Stem cell therapy can apparently improve. The erectile function of diabetic rats.[69] The possible mechanism of this effect may include the increase of the content of smooth muscle and endothelium.
Bone marrow MSCs	10 rats received mesenchymal stem cells (2×10^6 cells /rat), first dose (10^6 cells/ rat) and after one week, rats received the second dose of cells (10^6 cells/rat).	Diabetes in male Sprague Dawley (S.D) rats	Intravenous injection through penial vein perrat	The consequences of the present work uncovered that rodent bone marrow harbors cells that have the ability to recover the islets of Langer hanz and differentiate into useful insulin-secreting cells fit for controlling hyperglycemia, hyper lipidemia, and diverse adjusted parameters in diabetic rats. This may be useful in the avoidance of diabetic complications.[70]

Bone marrow-derived MSC	1× 10^6 MSCs per rat	Infertility in male rats	-----	MSCs have tremendous potential for regenerative medicine; MSCs/BM is capable of differentiating into germ cells and Ley dig cells in the testis. MSCs modulated the decline of serum testosterone levels induced by the lead treated group (LN) and approached within control values,especially at 60 days. Because Ley dig cells are responsible for testosterone production, stem cell transplantation may replace the need of life-long testosterone supplementation in male hypogonadism. In addition, MSCs modulated DNA apoptosis in sperm and testicular tissues. These results show that MSCs could be both a rich and functional source for the Treatment of infertility.[71]

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