

STEM CELL AND ITS THERAPY**Thakur P*, Sood M, Sharma RB, Vashist H, Gupta A and Agarwal S**

L.R. Institute of Pharmacy, Solan (H.P.), 173223.

Article Received on
13 March 2017,Revised on 03 April 2017,
Accepted on 24 April 2017

DOI: 10.20959/wjpr20175-8421

Corresponding Author*Thakur P.**L.R. Institute of Pharmacy,
Solan (H.P.), 173223.**ABSTRACTS**

Stem cells are a class of undifferentiated cells that are able to differentiate into specialized cell types. Commonly, stem cells come from two main sources. Embryos formed during the blastocyst phase of embryological development and Adult tissue. Both types are generally characterized by their potency, or potential to differentiate into different cell types such as skin, muscle, bone, etc Adult or somatic stem cells exist throughout the body after embryonic development and are found inside of different types of tissue. These stem cells have been found in tissues such as the brain, bone marrow,

blood, blood vessels, skeletal muscles, skin, and remain in a quiescent or non-dividing state for years until activated by disease or tissue injury. The adult stem cells can divide or self-renew indefinitely, enabling them to generate a range of cell types from the originating organ or even regenerate the entire original organ. This latter mass is the source of embryonic stem cells totipotent cells (cells with total potential to develop into any cell in the body). Many common neurological disorders, such as Parkinson's disease, stroke and multiple sclerosis, are caused by a loss of neurons and glial cells. In recent years, neurons and glia have been generated successfully from stem cells in culture, fueling efforts to develop stem-cell-based transplantation therapies for human patients.

KEYWORDS: stem cells, totipotent, generate, disease.**INTRODUCTION****What Are Stem Cell**

Stem cells are a class of undifferentiated cells that are able to differentiate into specialized cell types. Commonly, stem cells come from two main sources:

- a) Embryos formed during the blastocyst phase of embryological development (embryonic stem cells) and

b) Adult tissue (adult stem cells).

Both types are generally characterized by their potency, or potential to differentiate into different cell types (such as skin, muscle, bone, etc.). A cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissue, is thus called a stem cell.

Stem Cell Characteristics

- 'Blank cells' (unspecialized)
- Capable of dividing and renewing themselves for long periods of time (proliferation and renewal)
- Have the potential to give rise to specialized cell types (differentiation).

Table 1: Kinds of stem cell.

Stem cell type	Description	Examples
Totipotent	Each cell can develop into a new individual	Cell from early (1,3days) embryos
Pluripotent	Cell can form any (over 200) Cell type	Some cells of blastocyst (5 to 14) days
Multipotent Tissue, Cord	Cell differentiated, but can Form a number of other tissues	Fetal Blood, and adult stem cells

Source of Stem Cells

Adult Stem Cell

Adult or somatic stem cells exist throughout the body after embryonic development and are found inside different types of tissue. These stem cells have been found in tissues such as the brain, bone marrow, blood, blood vessels, skeletal muscles, skin, and the liver. They remain in a quiescent or non-dividing state for years until activated by disease or tissue injury.

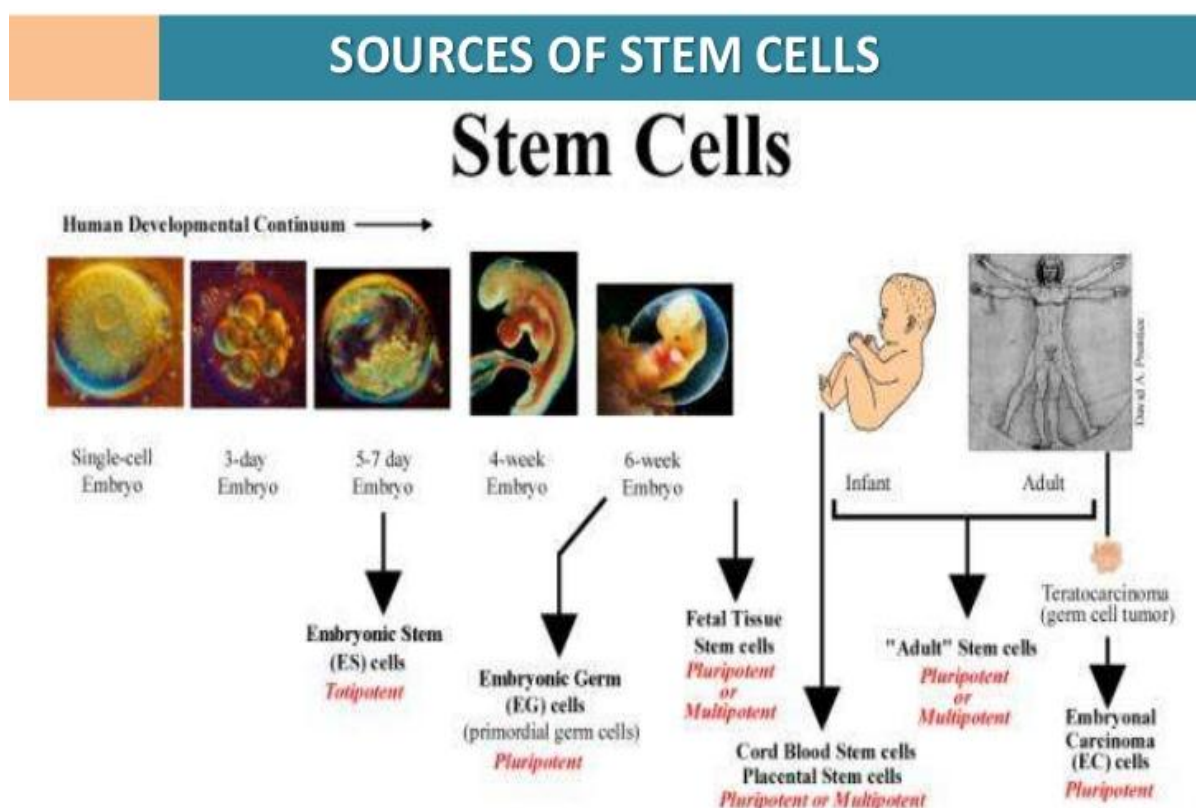
Adult stem cells can divide or self-renew indefinitely, enabling them to generate a range of cell types from the originating organ or even regenerate the entire original organ. It is generally thought that adult stem cells are limited in their ability to differentiate based on their tissue of origin, but there is some evidence to suggest that they can differentiate to become other cell types.^[1,2]

Embryonic Stem Cell

For many years, the difficulties encountered in accessing peri-implantation embryos limited study of the cellular interactions that occur during the initial stages of mammalian

development. Therefore, *in vitro* techniques were developed to circumvent this problem. Pluripotent embryonic stem (ES) cells, like embryonal carcinoma cells before them, were first used as a means to examine in detail early differentiation. However, the properties of ES cells identified them as being highly suitable for the generation *in vitro* of specific cell lineages. ES cells are harvested from the inner cell mass of the pre-implantation blastocyst and have been derived from rodents primates and human beings. Murine ES cells remain undifferentiated when grown in the presence of leukaemia inhibitory factor (LIF) and, for some lines, culture on murine embryonic fibroblasts (MEFs). LIF does not have the same effect on human ES cells and, in order to maintain them in an undifferentiated state, these require culture on MEF feeder layers in the presence of basic fibroblast growth factor (bFGF), or on Matrigel or laminin in MEF-conditioned medium. When LIF or feeder cells are withdrawn, most types of ES cells differentiate spontaneously to form aggregates known, in view of their similarity to post-implantation embryonic tissues, as embryoid bodies. These spherical structures are comprised of derivatives of all three germ layers. Synchronous formation of embryoid bodies, a prerequisite for gene expression studies of differentiating ES cells, can be achieved by removal of the feeder cell layer or LIF followed by suspension culture (hanging drop method) or by cultivation in methyl cellulose-containing medium.^[3]

Table 2: Source Of Stem Cell^[5]



Mechanism of Stem Cell Therapy

The human body keeps a supply of stem cells available to help repair injured and degenerated tissues at all times, making it fairly simple to retrieve them for therapeutic purposes. Stem cells remain in reserve, in the marrow cavity of bones.

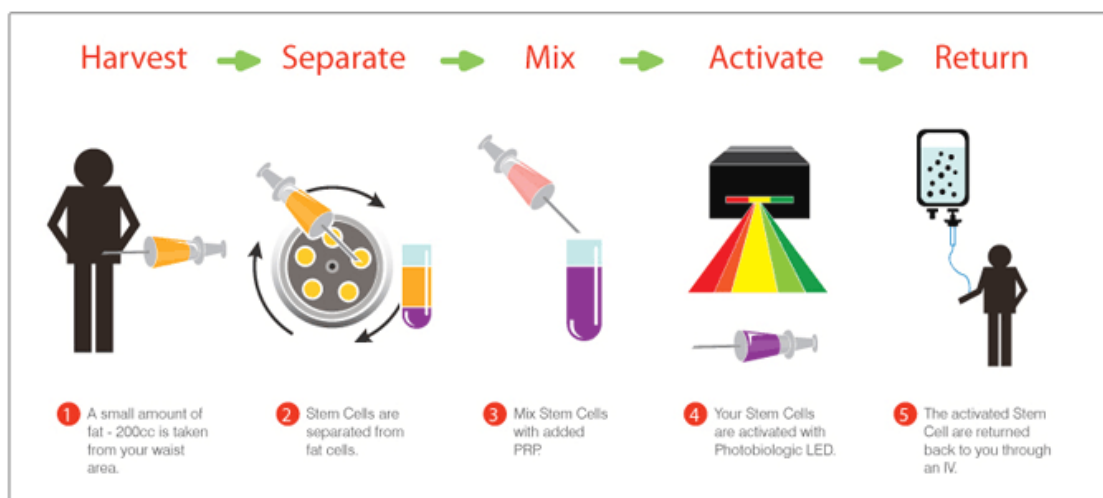


Figure 1: Mechanism of stem cell therapy.^[6]

The procedure is done under ultrasound or x-ray precision and guidance. A special needle is inserted into the bone to withdraw marrow blood, which contains the stem cells. This harvesting procedure is not considered difficult as it is not painful.

After bone marrow blood is drawn, it is taken to our laboratory and centrifuged to concentrate and purify the stem cells while other cells that are not needed are removed, leaving a concentrated sample of stem cells used to help heal your injury.

The entire process is done by hand to enable customized designing of the stem cell specimen for your particular injury. A preparation of concentrated platelets is also gathered at this time for injection into the injury site to release growth factors that triggers the stem cells that will later be injected. These platelets are injected again 3-5 days later to keep the stem cells activated and provide additional healing.

Stem Cell Transplantation

A stem cell transplant can be used to infuse healthy stem cells into the body to stimulate new bone marrow growth, suppress the disease, and reduce the possibility of a relapse. Stem cells can be found in the bone marrow, circulating blood (peripheral blood stem cells), and umbilical cord blood.

Two main types of stem cell transplants:

- Autologous stem cell transplant
- Allogeneic stem cell transplant

The stem cell transplant process

Before a stem cell transplant, it will undergo a conditioning regime, which involves intensive treatment to destroy as many cancer cells as possible. You may receive high doses of chemotherapy and, in some cases, radiation therapy. Once this preparative regime is complete, you're ready to undergo the transplant. Much like a blood transfusion, you'll receive the stem cells intravenously. The procedure takes about an hour. After entering the bloodstream, the stem cells travel to the bone marrow and start to make new blood cells in a process known as engraftment. In the months following the transplant, your care team will monitor your blood counts. You may need transfusions of red blood cells and platelets. Sometimes, the intensive treatments you receive before the stem cell transplantation can cause side effects, like infection. In this case, doctor may administer IV antibiotics.

If there is allogeneic stem cell transplant, doctor may prescribe certain drugs to reduce the risk of graft-versus-host-disease (GVHD), a condition where the donated cells attack the patient's tissue^[7]

Application of Stem Cell

Tissue Repair

Regenerate spinal cord, heart tissue or any other major tissue in the body.

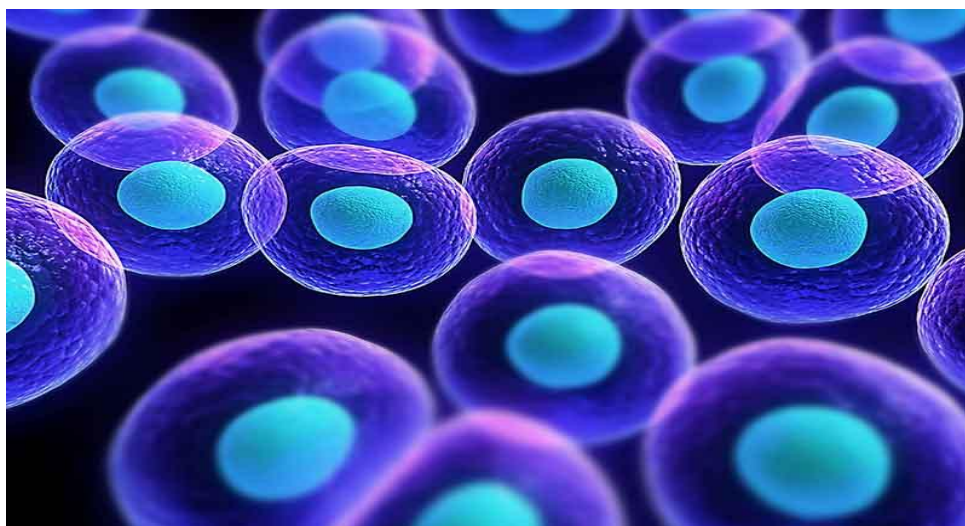


Figure 2: Tissue repair.^[8]

Use of Stem Cells in Neurological Treatment

Many common neurological disorders, such as Parkinson's disease, stroke and multiple sclerosis, are caused by a loss of neurons and glial cells. In recent years, neurons and glia have been generated successfully from stem cells in culture, fueling efforts to develop stem-cell-based transplantation therapies for human patients. More recently, efforts have been extended to stimulating the formation and preventing the death of neurons and glial cells produced by endogenous stem cells within the adult central nervous system. The next step is to translate these exciting advances from the laboratory into clinically therapies.

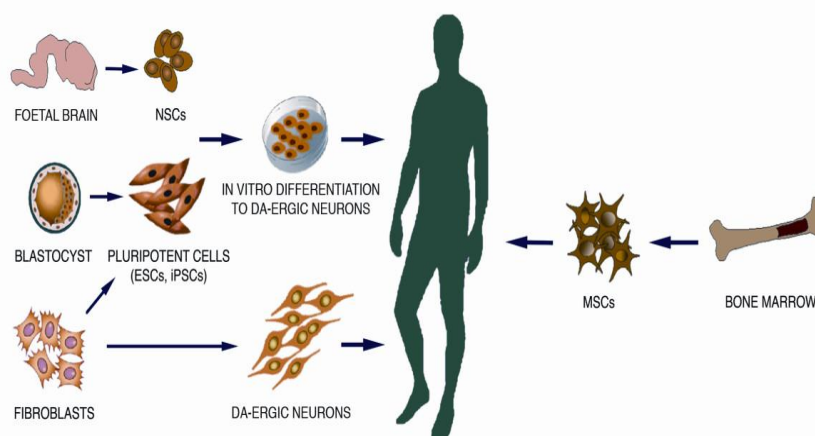


Figure 3: Schematic illustration of possible sources of stem cells for therapy in Parkinson's disease.

1) (A) Neural stem cells (NSCs) from human fetal brain, expanded and differentiated to DA-ergic neurons; 2) Pluripotent cells generated from blastocysts (ESCs) or fibroblasts (iPSCs), expanded and differentiated to DA-ergic neurons; 3) DA-ergic neurons generated by direct conversion of fibroblasts; 4) Bone marrow-derived mesenchymal stem cells (MSCs).^[9]

Stem Cell Therapy for Cardiac Disorders

Congestive heart failure (CHF) is a complex clinical syndrome that results from myocardial dysfunction that impairs the heart's ability to circulate blood at a rate sufficient to maintain the metabolic needs of peripheral tissues and various organs.

Heart failure is a relatively common clinical disorder estimated to affect more than 5 million patients in the United States. About 400,000 new patients are diagnosed with CHF each year.

Morbidity and mortality rates are high; annually, approximately 900,000 patients require hospitalization for CHF, and up to 200,000 patients die from this condition.

The average annual mortality rate is 40% to 50% in patients with severe (New York Heart Association [NYHA] class IV) heart failure. In the United States CHF treatment is estimated to cost more than 25 billion dollars for 2004.¹

The initial stages of heart failure are managed with medical therapy, and end-stage heart failure is managed with surgical procedures in addition to medical therapy.

Some of the proven surgical procedures include myocardial revascularization, ventricular assist devices, and heart transplantation.

2 Although surgical and catheter-based revascularization of ischemic myocardium can treat angina, reduce the risk of myocardial infarction, and improve function of viable myocardium.

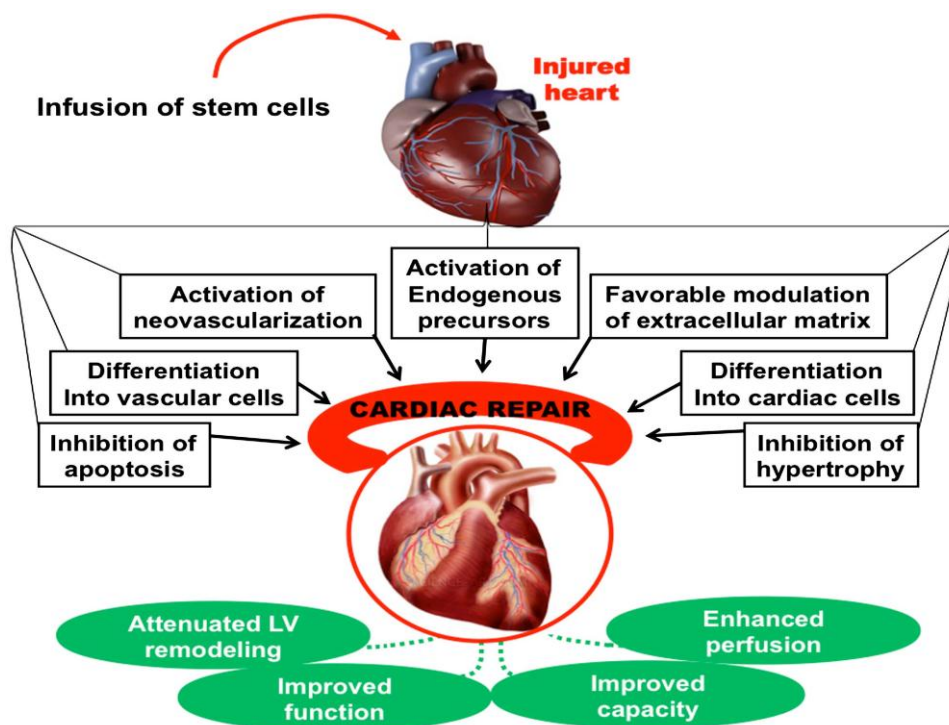


Figure (4) Cardiac repair by stem cell.^[11]

Heart failure is the leading cause of death worldwide, and current therapies only delay progression of the disease. Laboratory experiments and recent clinical trials suggest that cell-based therapies can improve cardiac function, and the implications of this for cardiac regeneration are causing great excitement. Bone-marrow-derived progenitor cells and other

progenitor cells can differentiate into vascular cell types, restoring blood flow. More recently, resident cardiac stem cells have been shown to differentiate into multiple cell types present in the heart, including cardiac muscle cells, indicating that the heart is not terminally differentiated. These new findings have stimulated optimism that the progression of heart failure can be prevented or even reversed with cell-based therapy.

Bone marrow is the spongy tissue found inside some of your bones, such as your hip and thigh bones. It contains immature cells (called stem cells), and these stem cells can transform themselves into the red blood cells that carry oxygen through your body, the white blood cells that fight infections and the platelets that help with blood clotting.

White Blood Cell Fight Infection

There are three very important types of white blood cells, essential to the proper functioning of the body's immune system:

Neutrophils and Macrophages- fight bacterial and fungal infections by "eating" germs.

Lymphocytes- fight bacterial, viral and fungal infections. T lymphocytes (also called T cells) attack viruses and other germs. T cells from the donor also result in a reaction called graft-versus-host-disease. T cells from the recipient can reject the donor bone marrow cell resulting in graft failure. B-lymphocytes make antibodies which help destroy germs in your body.

Red blood cells carry oxygen to tissues in the body.

Alternatives of Stem Cell Therapy

Blood that circulates in your veins and arteries contains stem cells

These stem cells are known as peripheral blood stem cells (PBSC). Patients who are recovering from chemotherapy and normal individuals who are treated with certain drugs that stimulate the growth of the bone marrow have relatively large numbers of PBSC in their blood. The PBSC can be collected and used in certain situations as a source of stem cells for transplantation.

Blood that is found in the placenta of a newborn baby once the umbilical cord is cut:

Umbilical cord blood has been successfully used as a source of bone marrow stem cells for transplantation in both related and unrelated patients. When your body is damaged by a disease or an injury (including the toxic effects of cancer drugs such as chemotherapy), stem cells are needed for the natural healing process of regeneration. Certain organs like the skin, gastrointestinal tract and bone marrow contain large numbers of stem cells and undergo

regeneration almost continuously. Organs like the brain, heart and pancreas are not populated by stem cells, and these organs rely on stem cells to circulate in the blood stream.

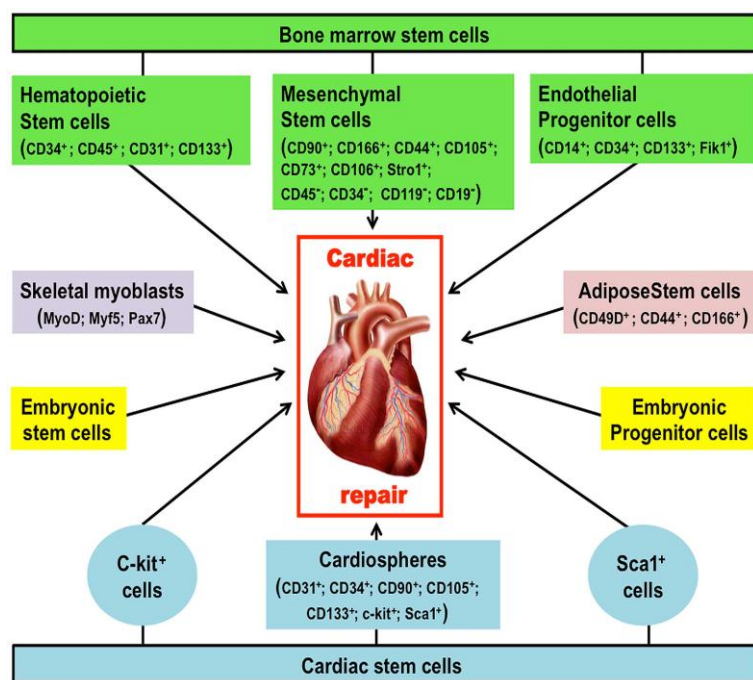


Figure 5: Bone marrow stem cell therapy for cardiac repair.

Treatment for Rheumatoid Arthritis By Stem Cell

Stem cell therapy for Rheumatoid Arthritis is being studied for efficacy in improving the complications in patients through the use of their own stem cells. These Rheumatoid Arthritis therapies may help patients who don't respond to typical drug treatment, want to reduce their reliance on medication, or are looking to try stem cell therapy before starting drug treatment. Stem cells that come from your adipose (fat) tissue have distinct functional properties including immunomodulatory and anti-inflammatory functional properties which have the capability of repairing and regenerating damaged tissue associated with disease and injury.

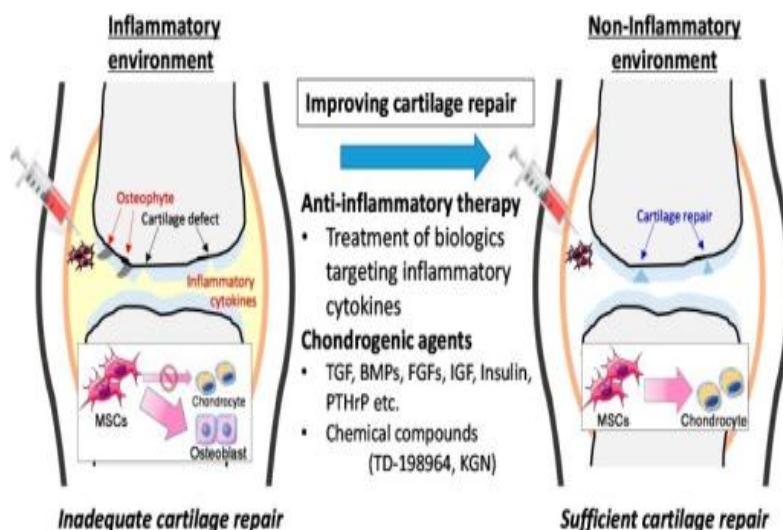


Figure 6: Stem cell therapy for cartilage repair in rheumatoid arthritis disease.^[13]

Treatment for Osteoarthritis Stem Cell

- The majority of complications in Osteoarthritis patients are related to the deterioration of cartilage that cushions the ends of bones in your joints. Cartilage is a firm, slippery tissue that permits nearly frictionless joint motion. In Osteoarthritis, this surface become rough. Eventually, if the cartilage wears down completely, patients will be left with bone rubbing on bone.
- Stem cell treatment provided by Stem Genex Medical Group is designed to target these areas within the joints to help with the creation of new cartilage cells. Mesenchymal stem cells are multipotent and have the ability to differentiate into cartilage called (chondrytes). The goal of each stem cell treatment is to inject the stem cells into the joint to create cartilage (chondrocyte cells). Stem cells are natural anti-inflammatories which can assist with Osteoarthritis pain and swelling in the joint area.

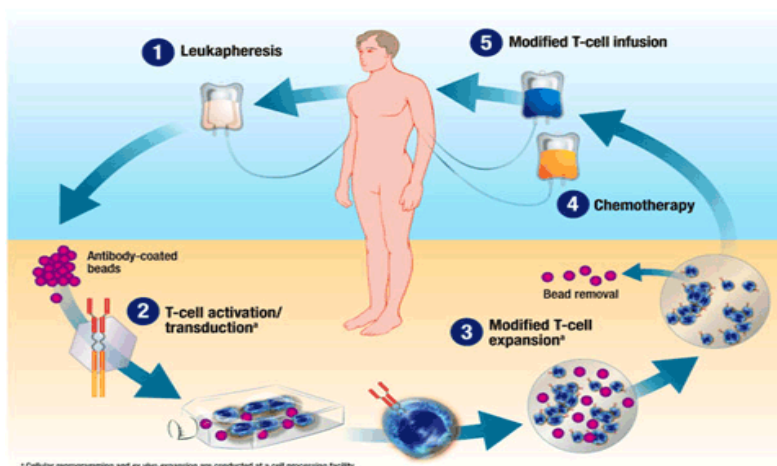


Figure 7: Stem cell therapy for osteoarthritis disorder.

Haematopoietic /Bone Marrow Stem Cell Transplant

Haematopoietic or blood-forming stem cells are immature cells that can mature into blood cells. These stem cells are found in the bone marrow, bloodstream, or umbilical cord blood. Bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) are procedures that help restore stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy.

There are two types of transplants

- **Allogeneic transplant:** Patients receive stem cells from their brother, sister or parent; or from an unrelated donor.
- **Syngeneic transplant:** Patients receive stem cells from their identical twin.

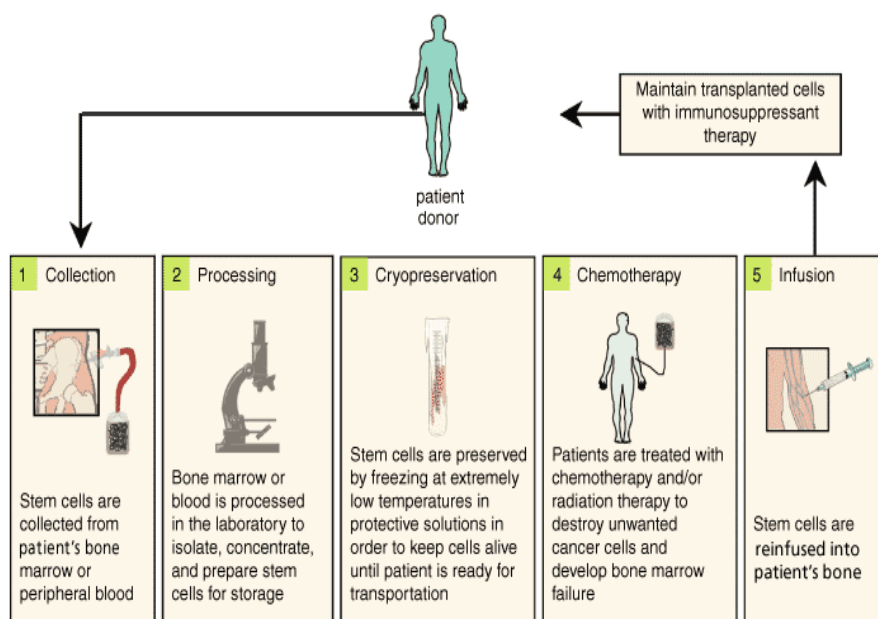


Figure 8: Stem cell therapy for bone marrow transplantation.^[15]

What is Cancer Stem Cell

An accurate definition is critical to enable researchers working in the same or different systems to compare cells exhibiting a common set of properties. The consensus definition of a cancer stem cell that was arrived at this Workshop is a cell within a tumor that possess the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor. Cancer stem cells can thus only be defined experimentally by their ability to recapitulate the generation of a continuously growing tumor. The implementation of this approach explains the use of alternative terms in the literature, such as "tumor-initiating cell" and "tumorigenic cell" to describe putative cancer stem cells. The idea that cancer is primarily driven by a smaller population of stem cells has important implications. For

instance, many new anti-cancer therapies are evaluated based on their ability to shrink tumors, but if the therapies are not killing the cancer stem cells, the tumor will soon grow back (often with a vexing resistance to the previously used therapy). An analogy would be a weeding technique that is evaluated based on how low it can chop the weed stalks—but no matter how low the weeds are cut, if the roots aren't taken out, the weeds will just grow back. Another important implication is that it is the cancer stem cells that give rise to metastases (when cancer travels from one part of the body to another) and can also act as a reservoir of cancer cells that may cause a relapse after surgery, radiation or chemotherapy has eliminated all observable signs of a cancer.

One component of the cancer stem cell theory concerns how cancers arise. In order for a cell to become cancerous, it must undergo a significant number of essential changes in the DNA sequences that regulate the cell. Conventional cancer theory is that any cell in the body can undergo these changes and become a cancerous outlaw. But researchers at the Ludwig Center observe that our normal stem cells are the only cells that reproduce themselves and are therefore around long enough to accumulate all the necessary changes to produce cancer. The theory, therefore, is that cancer stem cells arise out of normal stem cells or the precursor cells that normal stem cells produce.

Thus, another important implication of the cancer stem cell theory is that cancer stem cells are closely related to normal stem cells and will share many of the behaviors and features of those normal stem cells. The other cancer cells produced by cancer stem cells should follow many of the rules observed by daughter cells in normal tissues. Some researchers say that cancerous cells are like a caricature of normal cells: they display many of the same features as normal tissues, but in a distorted way. If this is true, then we can use what we know about normal stem cells to identify and attack cancer stem cells and the malignant cells they produce. One recent success illustrating this approach is research on anti-CD47 therapy.^[16]

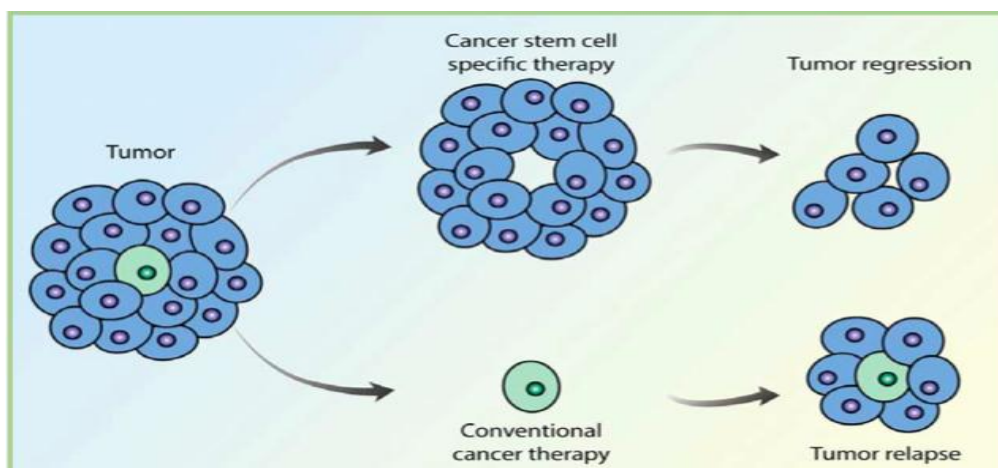


Figure 9: Stem cell therapy for cancer.^[17]

Therapy of Stem Cell for Type 2 Diabetes

- Pancreatic cells do not produce insulin
- Embryonic Stems Cells might be trained to become pancreatic islets cells needed to secrete insulin.

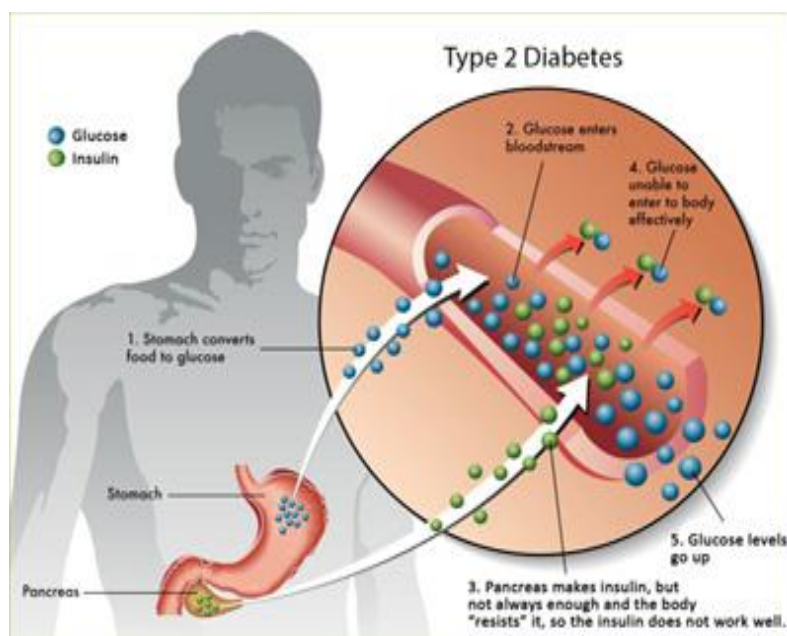


Figure 10: Stem cell therapy for type2 diabetes^[18]

Potential Uses of Stem Cell Therapy

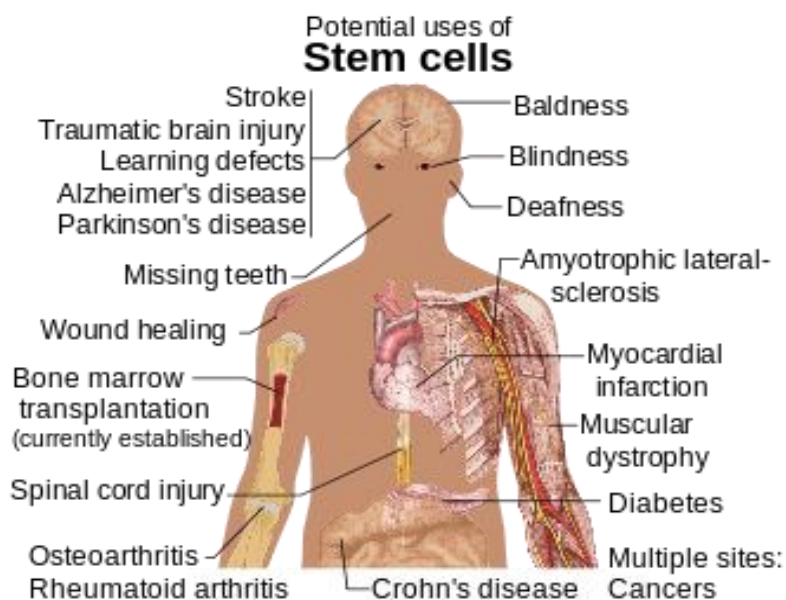


Figure 11: Potential uses of stem cell.^[19]

Pros of Stem Cell Therapy Include the Following

- It offers a lot of medical benefits in the therapeutic sectors of regenerative medicine and cloning.
- It shows great potential in the treatment of a number of conditions like Parkinson's disease, spinal cord injuries, Alzheimer's disease, schizophrenia, cancer, diabetes and many others.
- It helps the researchers know more about the growth of human cells and their development.
- In future, the stem cell research can allow the scientists to test a number of potential medicines and drugs without carrying out any test on animals and humans. The drug can be tested on a population of cells directly.
- The stem cell therapy also allows researchers to study the developmental stages that cannot be known directly through the human embryo and can be used in the treatment of a number of birth defects, infertility problems and also pregnancy loss. A higher understanding will allow the treatment of the abnormal development in the human body.
- The stem cell therapy puts into use the cells of the patient's own body and hence the risk of rejection can be reduced because the cells belong to the same human body.

Cons of Stem Cell Therapy Include the Following

- The use of the stem cells for research involves the destruction of the blastocytes that are formed from the laboratory fertilization of the human egg.
- The long term side effects of the therapy are still unknown.
- The disadvantage of adult stem cells is that the cells of a particular origin would generate cells only of that type, like brain cells would generate only brain cells and so on.
- If the cells used in the therapy are embryonic then the disadvantage is that the cells will not be from the same human body and there are chances of rejection.

The stem cell therapy is still under the process of research and there are a number of things that needs to be established before it used as a treatment line.^[20]

Advantages of Stem Cell

1. Immense Medical Benefits: The main purpose of researching stem cells is to asses their use in the medical field. It has been shown that they can be extremely beneficial in therapeutic cloning to treat chronic illnesses. They have also been a wonderful stepping stone into the advancement of regenerative medicines.

2. A Better Knowledge of Human Growth: By studying the very foundation of human growth, stem cells, in depth, scientists have been able to gain a much better understanding of how our bodies work. This is vital for advancing medicine, medical processes, and even cures for degenerative illnesses.

3. The Key To Reversing Aging: Stem cells are the key to regenerative processes, which could possibly be age reversal. By reviving organs in our body that have become old or worn out, you could essentially live forever or at least greatly prolong the lives of humans.

4. Cure Development Defects Before They Happen: Stem cell research doesn't just benefit the people walking around the earth, but also the ones that haven't been born yet. The effects of these cells on embryos could change the way that birth defects are treated. They could possibly be corrected before the child is even born, greatly improving their quality of life and chance of survival.

Disadvantages of Stem Cell

1. High Uncertainties: One of the largest issues that people have with stem cell research is just how risky and unknown it truly is. Major advancements still need to be made and new technology must be developed before it can be used in an efficient and safe way.

2. Unknown Side Effects: Since stem cells are still in their research phase, the true long term effects of their use is not known or understood. Using them could cause new illnesses and disease to develop, or even interfere with the natural functions of the body.

3. Playing God: The moral argument is another big one when it comes to this topic. Many people believe that altering the basic structure of a human's genes is putting hands somewhere they should not be. The moral issue is the most frequently argued.

4. Perpetuates Cloning of Humans: Cloning is the process of making an exact genetic copy of a living organism. Stem cell research also aids the research into human cloning. Human cloning has been widely reviewed as a detriment to society with many negative benefits.^[21]

Therapeutic Uses of Stem Cell

The diverse literature on stem cell research comprises the work of basic and clinical scientists from many different subspecialties. This may account for the heterogeneous mixture of models, methods, types, quantity, and nature of the cells employed and the timing of experiments. Certain landmark findings and concepts should be highlighted, however, as they have shaped our understanding of what may be accomplished and what potential mechanisms may be explored to achieve clinically successful results in the future.

Paradigm Shift

The pivotal finding by Ashahara and colleagues¹ that postnatal vasculogenesis exists (ie, that stem cells contribute directly to the formation of new blood vessels in adults) provided new insights into mechanisms of cardiac repair. In the adult, neovascularization does not rely exclusively on angiogenesis (sprouting from preexisting blood vessels). Furthermore, endothelial progenitor cells (EPCs) that originate in the bone marrow play a role in vasculogenesis (physiological and pathological) and circulate in adult peripheral blood.¹ The intriguing observation in heart transplant patients that putative stem cells and progenitor cells from a recipient were present in the transplanted heart further supports the notion of ongoing

regenerative and reparative mechanisms mediated by circulating stem cells from the bone marrow.^[2]

- Tissue repair
 - nerve, heart, muscle, organ, skin
- Cancers
- Autoimmune diseases
 - diabetes, rheumatoid arthritis, MS

REFERENCES

1. http://www.medicalnewstoday.com/info/stem_cell.
2. http://www.medicalnewstoday.com/info/stem_cell.
3. Doetschman T, Williams P, Maeda N. Establishment of hamster blastocyst-derived embryonic stem cells. *Dev Biol*, 1988; 127: 224–227.
4. Annaconne PM, Taborn GU, Garton RL, Caplice MD, Brenin DR. Pluripotent embryonic stem cells from the rat are capable of producing chimeras. *Dev Biol*, 1994; 163: 288–292.
5. <https://image.slidesharecdn.com/roleofstemcellsinothopaedics-120826154359-phpapp02/95/stem-cells-in-orthopaedics-7-728.jpg?>
6. http://www.bangkokstemcells.com/wcontent/uploads/2015/05/Adistem_IV_diagram_Jun_1_2011-4.jpg
7. <http://www.cancercenter.com/treatments/stem-cell-transplantation>.
8. <http://livesicilia.it/wp-content/uploads/2017/02/invecchiamento-cellulare.jpg>
9. <http://bmcmmedicine.biomedcentral.com/articles/10.1186/>
10. Majka SM, Jackson KA, Kienstra KA, et al. Distinct progenitor population in skeleton muscle are bone marrow derived and exhibit different cell fates during vascular regeneration *J Clin Invest*, 2003; 111: 71-9.
11. https://www.spandidos-publications.com/article_images/ijmm/38/1/IJMM-38-01-0023-g01.jpg
12. https://www.spandidos-publications.com/article_images/ijmm/38/1/IJMM-38-01-0023-g00.jpg1
13. https://openi.nlm.nih.gov/imgs/512/391/4264224/PMC4264224_ijms-15-21270-g002.png3
14. <http://www.hopehealthandbeyond.in/wp-content/uploads/2016/04/StemCellTherapy5.gif>
15. <http://www.augusta.edu/cancer/patientcare/services-treatment/bmt/images/auto.gif>

16. <http://med.stanford.edu/ludwigcenter/overview/stemcells.html>,<http://med.stanford.edu/ludwigcenter/overview/theory.html>
17. http://static.projects.iq.harvard.edu/files/styles/os_files_xlarge/public/StemCellsCancerSCL2.png?
18. <http://www.giostar.com/wp-content/uploads/2015/12/Diabetes-II-Treatment-Giostar.jpg>
19. https://upload.wikimedia.org/wikipedia/commons/thumb/b/bd/Stem_cell_treatments.svg/330px-Stem_cell_treatments.svg.png
20. <http://www.healthguidance.org/entry/12366/1/Pros-and-Cons-of-Stem-Cell-Therapy.html>
21. <https://thenextgalaxy.com/advantages-and-disadvantages-of-stem-cell-research>.