

**A REVIEW ON STEM CELL THERAPY IN TREATMENT OF
DIFFERENT DISEASE****Shaikh Tarik*, Sonam Kukloria and Nandu Kayande**

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Corresponding Author*Shaikh Tarik**Thakur Shivkumarsingh
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Burhanpur (M.P.) India.**ABSTRACT**

This thesis present the information about stem cell and their use to cure the different disease related to cancer, Hodgkin and non Hodgkin lymphomea, diabetes, parkinsons disease, heart disease etc. This desseration also gives the information about the types of different stem cell such as bone marrow stem cell, adult stem cell, neural stem cell skin stem cell etc. The concept of regenerative medicine using the body's own stem cells and growth factors to repair tissues may become a reality as new basic science works and initial clinical experiences have "teamed-up" in an effort to develop alternative therapeutic strategies to treat the diseased myocardium. In particular, revealing the

signals that mediate cellular growth and differentiation may provide novel tools designed for myocardial regeneration in patients sustaining ischemic cardiomyopathy syndromes. Stem cells are a population of immature tissue precursor cells capable of self-renewal and provision of de novo and/or replacement cells for many tissues. Embryonic stem cells can be obtained from the inner cell mass of the embryonal blastocyst. Although it was recently shown that human embryonic stem cells can differentiate into cardiomyocytes, because of the immunogenicity and rejection, as well as ethical considerations, these cells may be restricted to experimental in vitro studies and their therapeutical potential remains to be determined. Also, these cells may act as an unanticipated arrhythmogenic source after intramyocardial transplantation.

KEYWORDS: Hodgkin Lymphomea, Embryonal blastocyst, Arrhythmogenic.**1. INTRODUCTION**

Stem cells are cells that have not yet developed into specialized cells. They have the ability to differentiate, meaning that they can become cells of any organ of the body. They can also

multiply to create new stem cells. Stem cells are generated in the bone marrow but are also present in our blood, as they are released from the bone marrow to the blood system. The regulators of stem cell growth at genomic and proteomic level were identified and we might be able to control stem cell in vitro.^[1]

The regenerative capability of a living creature was recorded as early as 330 BC although stem cell technology is just emerging; the regeneration of body parts is hardly a new concept, when Aristotle observed that a lizard could grow back the lost tip of its tail. From that time, there have been slow but steady attempts at understanding the regenerative capabilities of human being and it is only in the last 10 years that we have seen an information explosion in the area of stem cell research. Stem cells are likely to revolutionize the entire health care delivery.^[2]

Stem cell research is improving by leaps and bounds. These may soon become the basis for treating diseases such as Parkinson's disease, diabetes, heart failure, cerebral palsy, heart disease and host of other chronic ailments. Stem cells may also be used for screening new drugs and toxins and understanding birth defects without subjecting human volunteers to the toxins and drugs. Laboratory studies of stem cells enable scientists to learn about the cells' essential properties and what makes them different from specialized cell types. Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects.^[3]

1.1. Stem cell: Stem cells are the body's raw materials — cells from which all other cells with specialized functions are generated. Under the right conditions in the body or a laboratory, stem cells divide to form more cells called daughter cells.

These daughter cells either become new stem cells (self-renewal) or become specialized cells (differentiation) with a more specific function, such as blood cells, brain cells, heart muscle cells or bone cells. No other cell in the body has the natural ability to generate new cell types.^[4]

Stem cells are certain biological cells found in all multicellular organisms. They are in small portion in body mass, but can divide through mitosis and differentiate into diverse specialized cell types and can self renew to produce more stem cells. Different types of stem cells vary in

their degree of plasticity, or developmental versatility. Stem cells can be classified according to their plasticity and sources.^[5]

- **Embryonic stem cells:** Human embryos consist of 50–150 cells when they reach the blastocyst stage, 4–5 days post fertilization. Embryonic stem cells (ES cells) are derived from the inner cell mass of the blastocyst. They present two distinctive properties: they are able to differentiate into all derivatives of three primary germ layers (pluripotency), and they are capable of propagating themselves indefinitely, under defined conditions (Ying & Chambers, 2003).^[6]
- **Embryonic germ stem cells:** Embryonic germ (EG) cells are derived cells from primordial germline cells (PGCs) in early development. EG cells share many of the characteristics of human ES cells, but differ in significant ways. Human EG cells are derived from the primordial germ cells, which occur in a specific part of the embryo/fetus called the gonadal ridge, and which normally develop into mature gametes (eggs and sperm).^[7]
- **Fetal stem cells:** Fetal stem cells are primitive cell types found in the organs of fetuses. Fetal stem cells are capable 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 islet progenitors have been isolated in the fetuses (Beattie, et al., 1997). Fetal blood, placenta and umbilical cord are rich sources of fetal hematopoietic stem cells.^[8]

2. Sources of stem cells

There are several sources of stem cells. Pluripotent stem cells can be isolated from human embryos that are a few days old. Cells from these embryos can be used to create pluripotent stem cell "lines" —cell cultures that can be grown indefinitely in the laboratory. Pluripotent stem cell lines have also been developed from fetal tissue (older than 8 weeks of development). The two broad types of stem cells found in people are adult stems cells and embryonic stem cells.

Adult stem cells

- Cord blood, umbilical cord blood
- Bone marrow

- Blood, peripheral blood stem cells
- Menstrual blood
- Skin
- Teeth
- Placental tissue

All of these sources of adult stem cells share some characteristics. Others are unique and options are being researched daily. Embryonic stem cells

- Human embryos
- Fetal tissue.^[9]

3. Stem cell therapy

➤ Cell based therapy

The concept of cell-based therapy (or simply cell therapy, as it is sometimes called) is to repair, replace or supplement damaged or diseased cells with healthy cells. The work of Stem Cells scientists has already generated the means to supply stem cells, which upon transplantation, can differentiate into healthy new cells or tissues, and which may thereby be capable of alleviating or potentially even curing a broad array of intractable conditions.^[10]

➤ Stem cell transplantation

Stem Cell Transplantation is one of the innovative treatments offered at Apollo Hospitals. This facility is provided by Apollo Hospitals Ahmedabad and has shown steady growth since inception. Stem Cell Transplantation is an exciting area of medicine. It is a well established treatment for several cancers and diseases of blood since the last few decades.

Indications

- » Autologous Transplant (Stem Cells collected from one's own body)
- **Hodgkin's & Non Hodgkin's Lymphoma:** For relapsed/refractory cases, it is standard therapy and in most such cases, it is the only curative option.
- **Myeloma:** Although not curative, it is standard treatment as a part of initial therapy, as it prolongs survival substantially.
- **Leukemia:** Acute Myeloid Leukemia aspart of consolidation therapy, to increase chance of cure in this disease.

» Allogenic Transplant (Stem Cells collected from someone else's body)

- Thalassemia
- Several other genetic disorders, especially with single gene defects.
- Aplastic Anemia.
- Chronic Myeloid Leukemia
- High Risk AML & Relapsed AML
- Relapsed ALL (Acute Lymphocytic Leukemia)
- As an option in several advanced or refractory haematological malignancies eg. follicular lymphoma, CLL, myeloma etc.

4. Uses of stem cell

Stem cell transplant is an exciting area of medicine. It is a well established treatment for several cancers and diseases of blood, for the past few decades.

- **Diabetes (Type 1 & 2):** Stem Cell therapy is most effective treatment for diabetes mellitus because scientists have already proved that mesenchymal stem cells can be differentiated into pancreatic beta-islet cells after in-vitro culturing. Diabetes is metabolic and autoimmune disease means our body attacks to our own pancreatic cells as foreign cells so the treatment with autologous bone marrow derived mesenchymal stem cells (MSCs) provide immune-regulatory properties and stops the immune attack by secreting anti-inflammatory cytokines (IL-10, TGF-beta and IL-1). Stem cell treatment shows good improvement in diabetes patient because bone marrow derived stem cells concentrate (CD44+, CD31+, CD34+) has the capacity to regenerate the beta islets cells.^[11-12]
- **Acute/Chronic liver disease:** A lot of clinical trials have shown that Stem cell therapy is successful in liver related disorder like acute liver failure or end stage liver disease (ESLDs). So the concept is that stem cell has the potential to differentiate into hepatocyte cells after transplantation in liver disease and show improvement for all the evaluations in liver related disorder.^[13-14]
- **Muscular dystrophy:** There is no cure for Muscular Dystrophy but stem cell therapy mainly focuses on the inflammatory response in Muscular Dystrophy as a target for mesenchymal stem cell (MSC) therapy. In contrast to other cell based therapies attempted in DMD, Mesenchymal Stem Cells have the advantages to treat Muscular Dystrophy.^[15-16]

- **Stem cell therapy for COVID-19:** The coronavirus disease 2019 (COVID-19) global pandemic continues and antiviral agents and vaccines are currently under investigation. Mesenchymal stem cell (MSC)-based therapy can be a suitable option for management of patients with COVID-19 at the urgent time of virus outbreak. Currently, MSCs are being explored against the novel infectious disease due to their therapeutic properties of anti-inflammation, immunomodulation and tissue repair and regeneration, albeit the precise mechanisms of MSC action toward COVID-19 remain unclear. To date, rigorous results from clinical trials using MSCs in human have been weakly positive. The pervasive uncertainty of using MSC therapeutic products as an effective combatant against COVID-19 requires rigorous resolution on several fronts, including MSC fate after infusion, safety issue, homing capability, and MSC resistance to the disease microenvironment. Focusing on these facets, a few important ones will be critically analyzed and addressed in this article for the development of safe and effective MSC-based therapies for COVID-19.

TREATING COVID-19 WITH STEM CELL

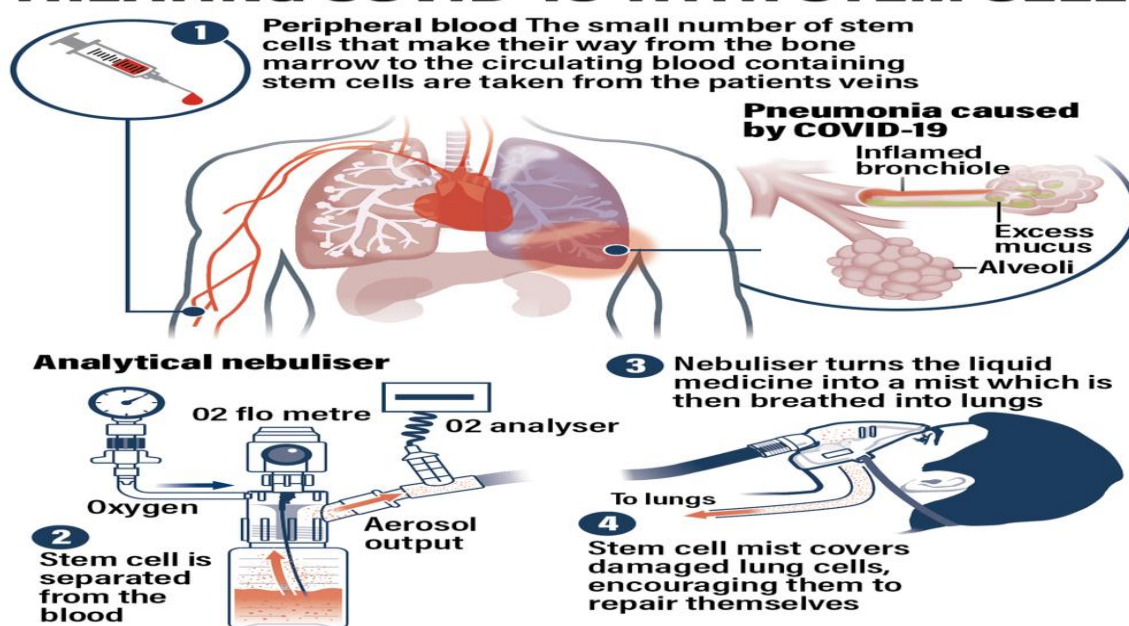


Fig. 1.

5. Stem Cells and Tissue engineering

Since stem cells are highly regulated by their microenvironment or the niche in which they reside, efforts are on to provide constructs that can mimic the cell milieu through development of tissue-engineered scaffolds^[74], These scaffolds also temporarily provide

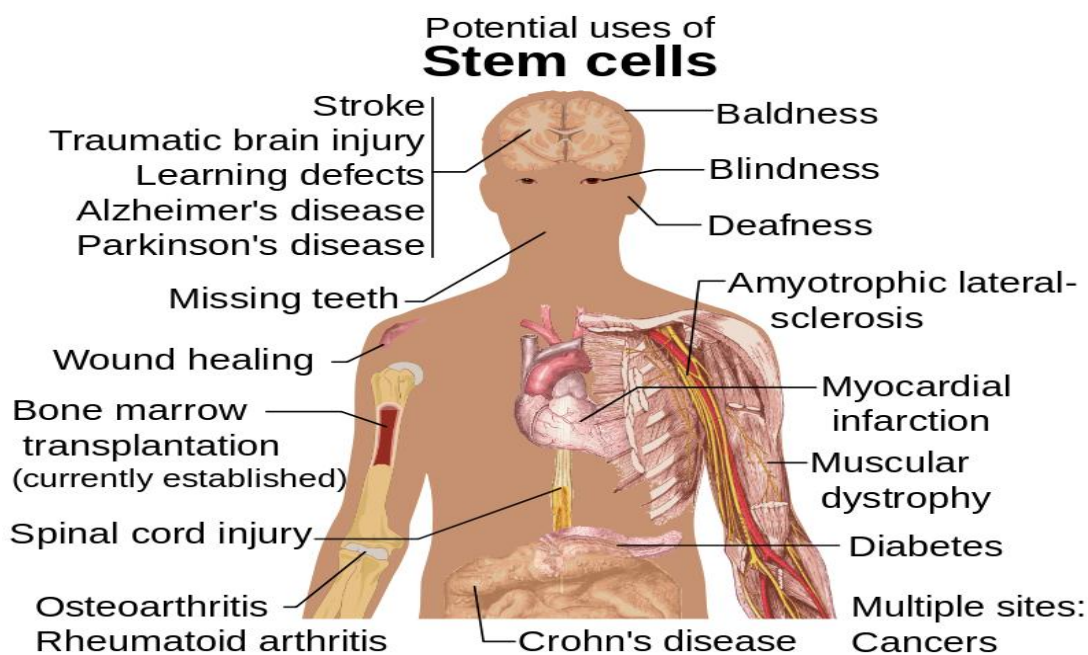
biomechanical support for cells until they are able to produce their own extra-cellular matrix.^[17]

Better control of the tissue formation process is an additional advantage. Scaffolds are typically fabricated by natural materials, which are inherently bioactive but lack mechanical strength, or synthetic materials, which lack inherent bioactivity but could be mechanically strong and can be fabricated with the desirable macro- (shape) and micro architecture (pore size, porosity). Numerous types of biomaterials both manmade or from natural sources are continually being discovered. Efforts are being carried out to modify the surface of these materials, to guide, and enhance stem cell differentiation. Initially, scaffolds were designed to be bio inert. Currently, biomaterials are made to interact with the cells that release growth factors, genes, or other signals in a time-dependent manner. Based on these active biomaterials, the conventional two dimensional (2-D) culture models have now paved the way for three-dimensional (3-D) culture environments that mimic the *in vivo* environments more closely and hence are more conducive to regulating stem cell proliferation and differentiation. Elements of the extracellular matrix and stoma MSCs have gained increasing attention as potentially crucial mediators in developing and maintaining the characteristics of 3-D cell cultures. Fibrin alone or in combination with other materials has emerged as an important biological scaffold for stem cells to regenerate adipose tissue, bone, cardiac tissue, cartilage, liver, nervous tissue, ocular tissue, skin, tendons, and ligaments. Culture on fibrous biodegradable scaffolds that mimic basement membrane texture has resulted in an increased expansion of both HSCs and ESCs. Similarly, the immobilization of cell associated Notch ligand has shown to increase the selfrenewal of HSCs. A perfect tissue engineered scaffold is elusive at present. The scaffold should not only support attachment, spreading growth and differentiation of cells but also control inflammation and foreign body reaction. It should be biodegradable into non-toxic products, sterilizable and manufacturable.

6. Stem cell research in india

Stem cell research has gained considerable impetus in India in the recent years. Draft guidelines for stem cell research in the country have been formulated jointly by the Department of Biotechnology and Indian Council for Medical Research. Several groups are actively and enthusiastically pursuing the field with reasonably good results. At Christian Medical College (CMC), in Vellore, a total of 626 transplants have been performed in 595 patients, with 28 patients having more than one transplant from October 1986 to December

2006.^[80] Besides, CMC Vellore, autologous and allogenic bone marrow or blood stem cell transplantation is being performed at other hospitals such as All India Institute of Medical Sciences (AIIMS), New Delhi and Tata Memorial Hospital, Mumbai.^[81,82] AIIMS has also set up the country's first cord blood bank for isolation of cord blood stem cells for in-house patients. At the L V Prasad Eye Institute, Hyderabad, transplantation of autologous cultivated limbal stem cells in patients with limbal stem cell deficiency, has shown a successful outcome with a stable ocular surface without conjunctivalization.^[18]



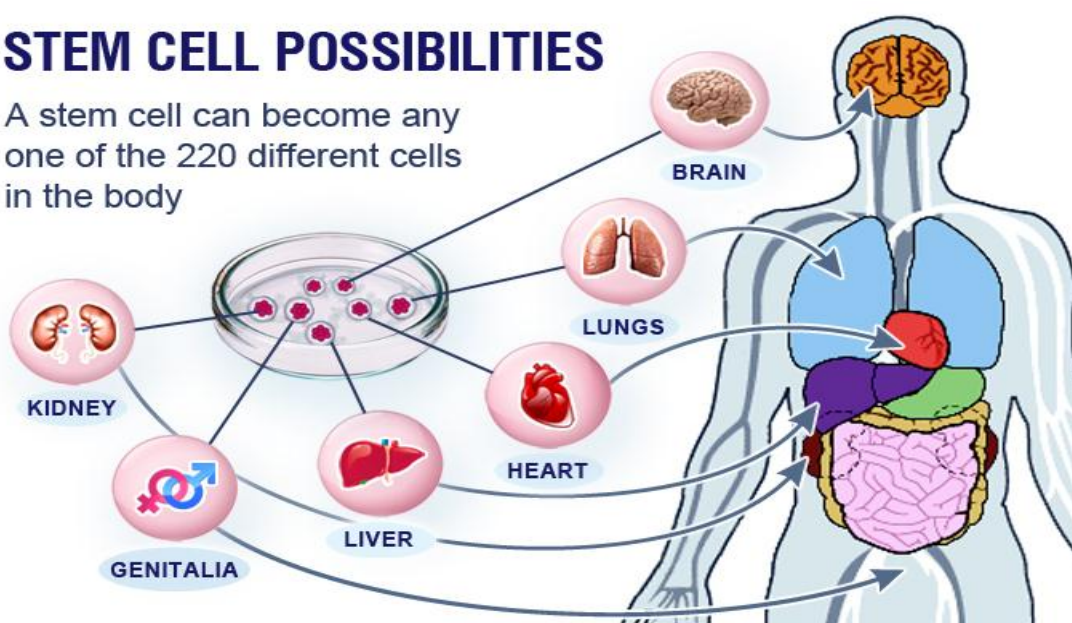
7. Current Challenges and Future possibilities

Besides the overwhelming promise of stem cells in various cellular therapies, their clinical and practical use is constrained by several technical and ethical issues. The biggest hurdle for the clinical use of adult stem cells is the small number of cells that can be isolated from any adult tissue. The identification of cells and factors in the so called 'stem cell niche' affecting the growth and differentiation of resident adult stem cells may be one possible answer. For example, the bone marrow stromal cells are known to promote proliferation and differentiation of HSCs in long-term cultures. The other approach is based on introduction of genes in the supporting feeder layer of cells that inhibits differentiation of target cells. The upregulation of notch ligands such as Jagged-1 and Delta in the stromal cells by gene modification strategies has been demonstrated to promote the expansion of stem cells without inducing differentiation. Another technique actively pursued is the usage of modified stem cells. Based on our understanding of the molecular pathways responsible for self-renewal and

proliferation of stem cells as well as discoveries of new genes that control stem cell proliferation and differentiation, novel strategies have come up. For example, HOX genes that are expressed during early development and which govern various processes including bodypart patterning have been shown to increase the selfrenewal potential of HSCs.^[102] Destruction of life in the form of an embryo has been a major ethical objection in embryonic stem cell derivation and research in several western countries. One way that has been suggested to circumvent the objection is to fuse existing hESCs with an adult somatic cell, generating a cell line that retains ESC specific properties and yet has the genotype of the somatic cell.^[103] There is however no technology available at present to selectively remove all the ESC chromosomes while retaining the somatic cell chromosomes. Development of such a technology is potentially expensive and will presumably take many more years. Other approach is the generation of induced pluripotent cell lines from induced somatic cell dedifferentiation. In this method, the adult somatic cells are genetically modified and reprogrammed to undergo a process of dedifferentiation. Availability of methods for growth and maintenance of ESC in culture present another major obstacle to their potential clinical use. Conventionally, hESC lines are grown in a medium containing animal serum as a source of nutrients and growth factors and then on mouse-derived fibroblast as feeder layers. The use of any cell based therapeutic agent in humans must however be free of animal contamination. In this direction, some laboratories have successfully cultured hESCs in a serum-free defined medium on human cellderived feeders or even in feeder free conditions.^[19]

STEM CELL POSSIBILITIES

A stem cell can become any one of the 220 different cells in the body



The risk of tumor formation following transplantation of hESC is another factor to be considered. Studies with both ESCs and ES derived differentiated cells have shown that they can form teratocarcinomas in adult mice if injected subcutaneously, intramuscularly or into the testis.^[106,107] The suitability of ESCs for transplantation purpose has also been skeptical because of the observed genetic instability of cloned cells and extreme inefficiency of the process.^[108] Allergucci et al recently reported that hESCs could undergo epigenetic changes over time in culture.^[109] All these observations indicate the need for optimization of procedures and periodic monitoring of the cell lines to ensure their genetic stability and hence suitability for in vivo applications. Finally, immunological issues are a major concern for allogenic stem cell transplantations with both adult and embryonic stem cells from nonautologous sources. Rejection can be inhibited by the use of immunosuppressive drugs, which can have serious side effects. Technologies to develop individual-specific stem-cell lines through somatic cell nuclear transfer or cell fusion may allow engineered stem cells containing the individual's own genetic material to be used for treatment.^[120]

8. DISCUSSION

Stem cells seem to have significant potential to treat COVID-19. Such treatments may decrease the burden on the health system of countries by curing the patients quickly. Due to exponential increase in the number of deaths due to COVID-19, scientists seem inclined to test any available interventions such as stem cell therapy. MSCs may possibly be a good option for COVID-19 patients, as stem cells are readily available in large numbers from different tissues, MSC can be cryopreserved until needed, and MSC characteristics and potential have been studied widely in preclinical and clinical studies. However, there are certain apprehensions that must be addressed before starting such a therapy, and during and after the therapy. Furthermore, there is a need for discussion of results obtained from such trials in a rapid manner so that the FDA might fast-track stem cell therapy as an approved emergency therapy for COVID-19.

9. CONCLUSION

As we know, stem cells have the following features. First, self-renewal is the hallmark property of stem cells in normal and diseased tissues. Second, the cells that continue to divide over long periods of time are much more likely to accumulate mutations that cause neoplasia and other diseases. Third, in normal tissues that contain self-renewing stem cells, such as the epithelia, the genetic changes which may cause tumorigenesis probably also occur in the stem

cell in progeny that acquire the potential for self-renewal. Finally, self-renewing of stem cell is controlled by distinct signalling pathways in different tissues. All the characters of stem cells promote the researches on culture, isolation, clinical application, and other related technologies.

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