Review Article CODEN: IJPRNK ISSN: 2277-8713
B. Oza, IJPRBS, 2015; Volume 4(6): 122-136 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

EMERGING APPLICATIONS OF STEM CELL THERAPY: A REVIEW

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Accepted Date: 05/11/2015; Published Date: 27/12/2015

Abstract: An ever increasing demand for organ transplant to fight the life threatening diseases has led to the need for novel and effective therapies and stem cell therapy is one such boon to meet these demands. Stem cell-based therapies are also known as cell-replacement therapies or regenerative medicine. Current regenerative medicines use stem cells to make functional tissues and organs to repair the defects and dysfunctionalities of the tissues and organs in the body. These defects may be congenital, caused due to any disorder or can be age related. Stem cells perform the renewal process by reaching injured sites in the organ and regenerate new cells. Regenerative medicine aims to restore normal function by repairing or replacing damaged or malfunctioning cells and tissues in patients. There are a variety of evidences available that highlight the role of stem cells in defeating many life threatening diseases and hence stem cell-base therapy would form a vital part of the modern medical care system. This review article brings to light the history of stem cells, their classification, properties, characteristics, its prospective therapeutic applications and brief overview of the regulatory status of stem cells in Europe, USA, and India.

Keywords: Stem Cells, Regenerate, Cell-Replacement Therapy, Renewal, Prospective Applications

PAPER-QR CODE

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Access Online On:

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How to Cite This Article:

B. Oza, IJPRBS, 2015; Volume 4(6): 122-136

INTRODUCTION

Cells are the building blocks of human body and some of them possess the ability to produce other cells, was an interesting discovery made during the mid 1800's. During the 1900s efforts were made to fertilize the mammalian eggs outside the human body. The first bone marrow transplant was successfully performed to treat siblings with severe combined immunodeficiency.

Other events in the development of stem cell therapy:

- 1978: Stem cells were discovered in human cord blood
- 1981: First in vitro stem cell line developed from mice
- 1988: Embryonic stem cell lines created from a hamster
- 1995: First embryonic stem cell line derived from a primate
- 1997: First Cloned lamb from stem cells
- 1997: Leukemia origin found as hematopoietic stem cell, indicating possible proof of cancer stem cells
- 1998: Isolated cells from the inner cell mass of early embryos and developed the first embryonic stem cell lines
- Today: Numerous studies are being carried out to exploit other varied uses of stem cells, whereas the adult stem cells are already being used to treat heart ailments and blood cancer. [1]

Regenerative medicine is an upcoming branch of research in molecular biology and tissue engineering which deals with the process of repairing, regenerating human cells and tissues to fix any abnormal functioning in the body. [2] Stem cell studies can help researchers in better understanding of the diseases occur, generate healthy cells to displace the diseased cells, stem cells can be guided into becoming specific cells that can be used to replace damaged tissues.

Stem cell therapy can be used to cure spinal cord injuries, Parkinson's disease, Alzheimer's disease, Cancer, Burns, and Type I diabetes [3] and hence they are believed to revolutionize the entire health care system. Due to the extraordinary growth in the field of molecular and cellular biology and the paradigm shifting towards cell-replacement therapy it's time for us to familiarize ourselves with stem cells, its characteristics and rapidly increasing uses.[4]

What are Stem cells?

Basic definition for stem cells goes as follows: They are undifferentiated cells with the ability to divide into specific cells via mitosis to produce more number of stem cells. [5] Stem cells act as human body's raw materials because from them all the other cells having particular functions are generated. [3]

All multicellular organisms possess stem cells. Each and every multicellular plant and animal rely on stem cells for growth from a single cell into an adult. The worn out and damaged cells in the human body are continually replaced by the stem cells and hence this makes bone healing and replacement of damaged skin due to cuts, wounds or burns easier and faster. [6] They are the "mother cells" having the potential to develop into any specific cells like cells of blood, heart, bones, skin, muscles, brain etc. [7]

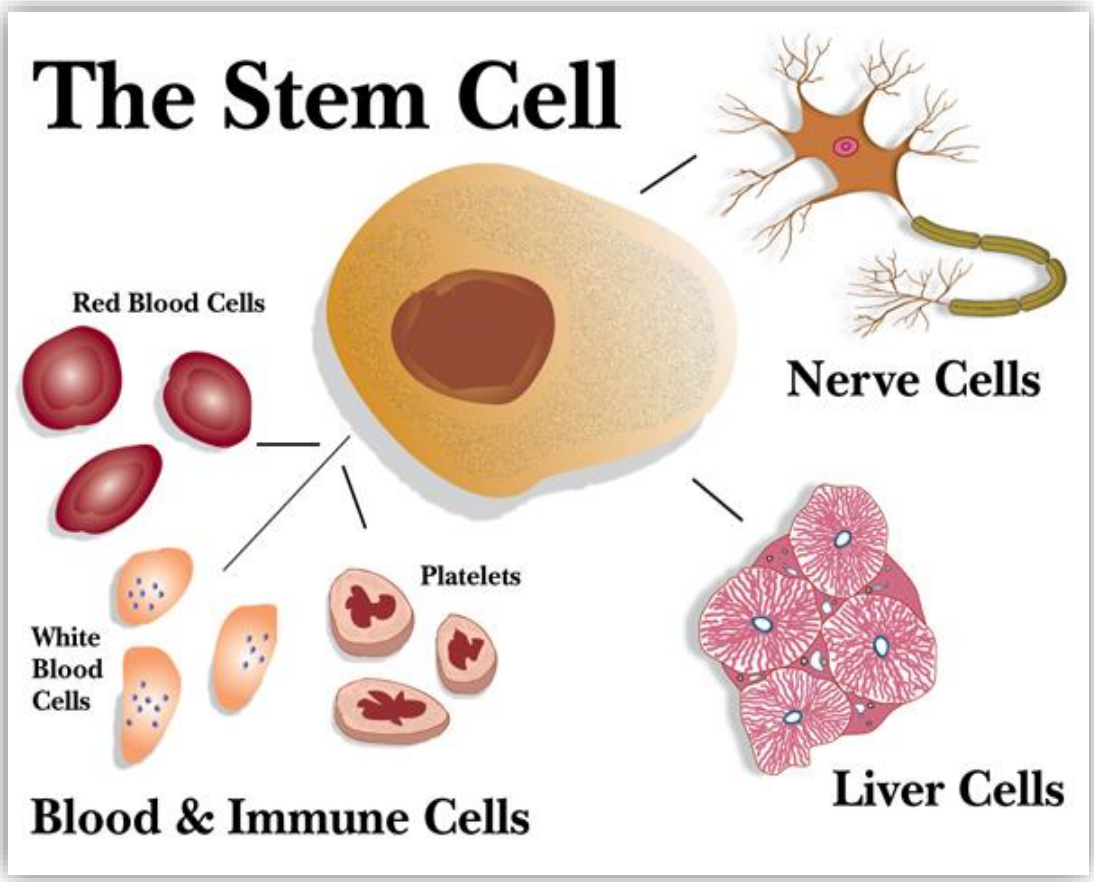

Fig. No. 1- Stem cell and its differentiation [8]

Following and injury, a stem cell self-renews by undergoing mitosis and gives rise to one daughter cell and one progenitor cell- it is an intermediate cell before it achieves a fully differentiated state.

Cellular developmental pathway of stem cells is as directed:

Stem cell → Progenitor cell + Stem cell → Differentiated cell. [4]

Characteristics of Stem cells: [4], [9]

Stem cells have certain unique properties like:

- Stem cells are capable of long term self-renewal i.e. they continuously divide to generate exact copies of themselves. Unlike the blood cells, muscles cells, nerve cells which do not usually replicate themselves; stem cells may replicate many times, or even proliferate.
- One of the basic properties of stem cell is that it doesn't have any tissue specific structure and thus it can perform specialized functions. For example, a stem cell cannot work with a heart muscle cell to pump blood through the body, and unlike a red blood cell it cannot carry oxygen molecules through the bloodstream. However, unspecialized stem cells can give rise to specialized cells, like heart muscle cells, blood cells, or nerve cells.
- They have a fundamental property where in unspecialized stem cells give rise to specialized cells, and the process is called differentiation.
- Totipotency: They can generate all types of cells including germ cells (ESCs).
- Pluripotency: Generate all types of cells except cells of the embryonic membrane.
- Multipotency: They differentiate into more than one mature cell (MSC).

Types of Stem cells:

There are many different types of stem cells in the human body and each cell plays a vital and distinctive role in human growth and development. There are stem cells which exist only for a limited period such as during the development of an embryo while certain stem cells are found only in particular regions in the body such as the hair follicles or liver. Depending on the location and purpose stem cells differentiate into other cells. [6]

- Embryonic stem cells (ESCs):

Human embryos consist of 50–150 cells when they reach the blastocyst stage, 4-5 days post fertilization. The blastocyst is a very small ball of about 150 cells with a diameter of ~0.2 mm.

ESCs are derived from the inner cell mass of the blastocyst. They have two distinctive characteristics:

1. Pluripotent: Pluripotentcy means ESCs can differentiate into all cell types in the human body. During gastrulation they can eventually differentiate into all derivatives of three primary germ layers i.e. ectoderm, endoderm, mesoderm and these include each of the more than 220 cell types in the adult body. This property of ESCs differentiates them from the adult stem cells which are multipotent and can produce only a limited number of cell types. [11] ESCs possess the ability to divide for long periods and retain its ability to form new cells in an organism. [12]

2. Propagation: The Embryonic stem cells, under certain defined conditions are capable of propagating themselves indefinitely and in an undifferentiated state and can also differentiate when necessary. This makes the ESCs useful for both research and regenerative medicine, because they can reproduce infinite numbers of themselves for continued research or clinical use.[12]

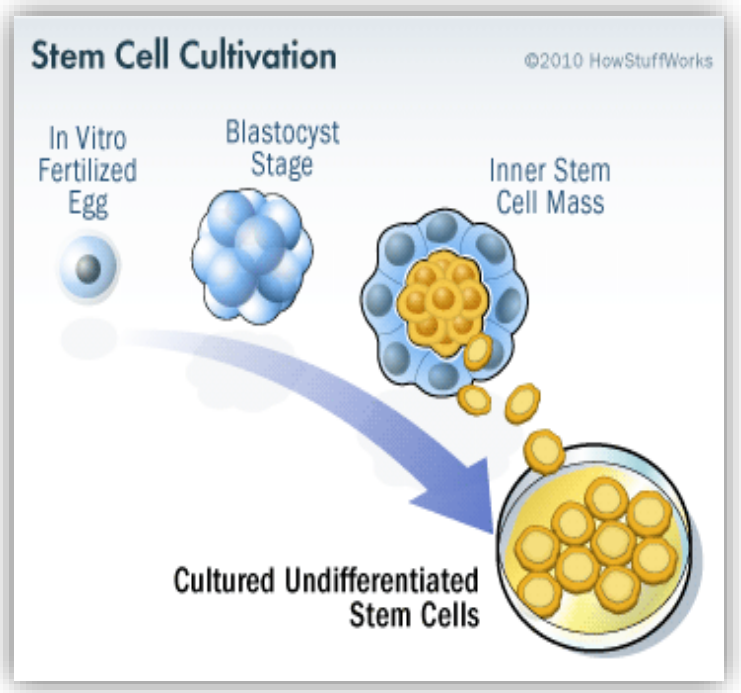

Fig. No. 2- Embryonic stem cells [13]

On January 23, 2009, Phase I clinical trials for transplantation of oligodendrocytes -a cell type of the brain and spinal cord derived from human Embryo stem cells into spinal cord-injured

individuals received approval from the U.S. Food and Drug Administration, marking it the world's first human Embryo stem cell human trial.[10]

Embryonic Germ (EG) cells have pluripotency similar to that of the embryonic stem cells. In humans, human Embryonic Germ (hEG) cells were first established in culture in 1998, shortly after the first human Embryonic stem cell (hES) cells, from tissue derived from an aborted fetus. They have been derived from 'primordial germ cells' that would ultimately form the gametes if the fetus had not been aborted. [1]

- Adult stem cells (ESCs):

Adult stem cells, also known as somatic stem cells are undifferentiated cells, found throughout the body after development, that multiply by cell division. Function of the adult stem cells is to replenish the dying cells and regenerate the damaged tissues. Some of the defining properties of adult stem cells are:

1. Self-renewal: It has the ability to undergo number of cycles for cell division while still maintaining it undifferentiated state.

2. Multipotency: Also known as multi differentiative potential, the ability to produce progency of quite a lot of distinctive cell types, unlike unipotency - a term applicable to cells that are limited to producing a single cell type. [15]

Scientists now have evidence that stem cells exist in the brain and the heart, two sites where adult stem cells were not at first expected to reside. Adult stem cells are found in many organs like blood vessels, teeth, heart, gut, liver. They reside in a specific area in the tissue called a "stem cell niche". Current evidence suggests that in many tissues stem cells are pericytes- the cells which compose the outer most layers of the blood cells. Also the stem cells might remain quiescent i.e. Non-dividing for long periods of time until they are activated by a normal need for more cells to repair the damage tissues

Differentiation pathway of normal stem cells: In humans, adult stem cells are capable of dividing, when needed, in turn giving rise to mature cell types that have characteristic shapes and specialized structures and functions of a specific tissue. The following are examples of differentiation pathways of adult stem cells (Fig. no. 3) that have been demonstrated *in vitro* or *in vivo*. [16]

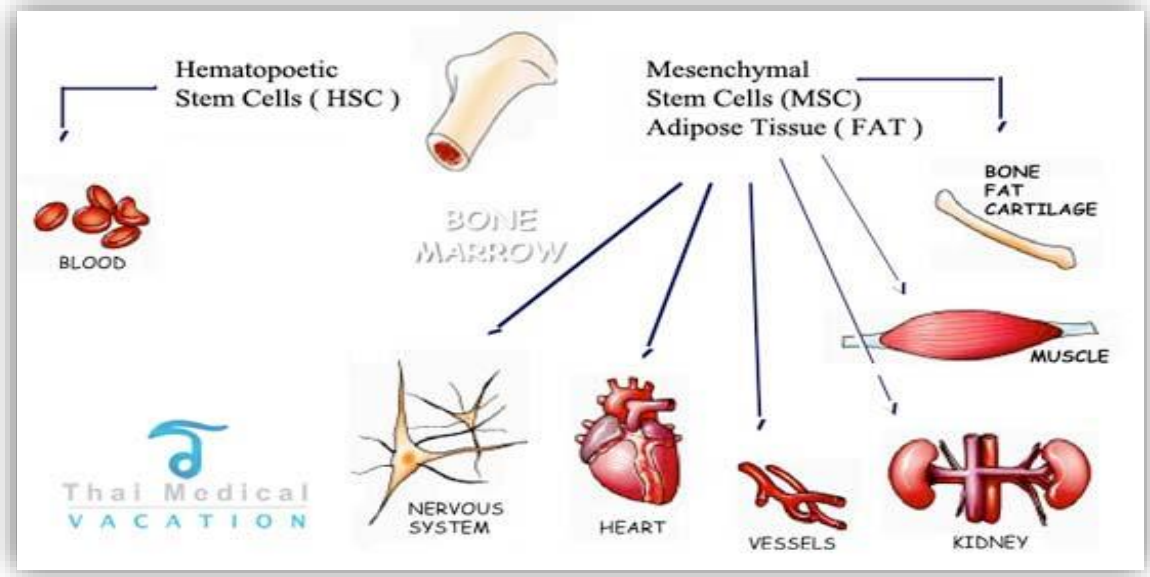

Fig. no. 3- Differentiation pathway of adult stem cells [17]

1. Hematopoietic stem cells: They give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, and macrophages. [16]

2. Mesenchymal stem cells: They are present in many tissues. Those from bone marrow e.g. bone marrow stromal stem cells, skeletal stem cells give rise to a variety of cell types: bone cells like osteoblasts and osteocytes, cartilage cells (chondrocytes), fat cells (adipocytes), and stromal cells that help in blood formation. [16]

3. Neural stem cells: They give rise to 3 main types of cell in the brain- nerve cells (neurons) and two categories of non-neuronal cells i.e. astrocytes and oligodendrocytes. [16]

4. Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells. [16]

5. Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer.

6. Mammary stem cells: They provide the source of cells for growth of the mammary gland during puberty. Mammary stem cells have been isolated from human and mouse tissue as well as from cell lines derived from the mammary gland. Single such cells can give rise to

luminal and myoepithelial cell types of the gland, and have been shown to have the ability to regenerate the entire organ in mice.[15]

7. Intestinal stem cells: They are located near the base of the stem cell niche called 'crypts of Lieberkuhn'. They divide continuously throughout life and use a multifaceted genetic program to produce the cells lining the surface of the small and large intestines. [15]

8. Olfactory adult stem cells: They have been successfully harvested from the human olfactory mucosa cells of the nose. Within the right chemical environment these cells can develop into many different cell types. They can be easily obtained and harvested without any harm to the patient. [15]

Therapeutic applications of stem cell therapy:

Application of stem cell based therapy in medicine is developing with time due to better understanding about cells, their differentiation pathways, and the ability of human stem cells to regenerate damaged organs and tissues. Stem cell based therapies, cell-replacement therapies or regenerative medicines are used to treat a number of diseases like Cancer, Diabetes, Heart diseases, Parkinson's disease, Nervous system diseases, Autoimmune diseases, etc.

1. Cancer:

Stem cell transplant -also called peripheral blood stem cell transplant is a treatment to try to cure some types of cancer, such as leukemia, lymphoma and myeloma. [18] In a typical stem cell transplant for cancer, high doses of chemotherapy are used with whole body radiation therapy with an aim to wipe out all the cancer cells. This also kills the stem cells in the bone marrow. Hence currently, bone marrow stem cells are used to rescue patients after chemotherapy and also to replace the destroyed cells. [19], [20] These stem cells are given directly into the vein and over the time they settle in the bone marrow and make healthy cells and the process is termed as engraftment.

There are 3 basic types of transplants. They are named based on who gives the stem cells.

- Autologous- the cells come from you (recipient's own)
- Allogeneic - the cells come from a matched related or unrelated donor
- Syngeneic - the cells come from your identical twin or triplet. [20]

<u>Autologus stem cell transplant:</u>

These stem cells are from the recipient only. In this case the cells are taken before the chemotherapy and radiation therapy destroys them. The cells are removed either from the

blood or bone marrow, then harvested and frozen. Primary advantage of autologus cell transplant is that you get your own cells and there is no risk of getting any graft versus host diseases or new infections from a new person. But the disadvantage of this kind of transplant is that there can be graft failure, and autologous transplants can't produce the "graft-versus-cancer" effect. Autologus cell transplants are mainly used for leukemia, lymphomas, multiple myeloma, testicular cancer and neuroblastoma, and certain cancers in children. [20]

Allogeneic stem cell transplants:

Among the most common type of allogenic cell transplant is where in the stem cells come from the donor whose tissue type closely matches the recipient's. Cord blood, is a newer source of stem cells for allogeneic transplant. Cord blood is the blood taken from the placenta and umbilical cord of newborns and is small volume of blood has a high number of stem cells that tend to multiply quickly. Advantages of this kind of transplant is the presence of "graft-versus-cancer" effect i.e. the donor stem cells make their own immune cells which can help in destroying any cancer cell that remains after high dose treatment, donor can be asked to donate more stem cells or even white blood cells if needed, and stem cells from healthy donors are free of cancer cells. Disadvantage of allogenic cell transplant is that the donor cells could die or be destroyed by the patient's body before settling in the bone marrow. Another risk associated is that the immune cells from the donor may not just attack the cancer cells – they could attack healthy cells in the patient's body. This phenomena is called "graft-versus-host disease"

Allogeneic transplant is most often used to treat certain types of leukemia, lymphomas, multiple myeloma, myelodysplastic syndrome, and aplastic anemia. [20]

Syngeneic stem cell transplants:

This is a special kind of allogeneic transplant that can only be used when the recipient has an identical sibling (twin or triplet). An advantage of syngeneic stem cell transplant is that graft-versus-host disease will not be a problem. A disadvantage is that because the new immune system is so much like the recipient's immune system, there is no graft-versus-cancer effect, either. Therefore, efforts must be made to destroy all the cancer cells before the transplant is done to prevent the cancer to relapse. [20]

2. Diabetes:

Glucose, produced by the liver and generated from the dietary carbohydrates is required by the human body for cell energy, central nervous system functioning and other vital functions. The amount of glucose in the blood and use of glucose is regulated by insulin (a protein hormone) produced by the beta cells in the islets of Langerhans of the pancreas. Type 1A diabetes is

caused by an autoimmune response and up to 90% cases of diabetes are type 1A. People with type 1A diabetes have little or no insulin production since the beta cells in the islets of Langerhans of the pancreas are damaged by their own immune system. When insulin production is affected, tight regulation of blood glucose concentration is lost because of which blood glucose level rises abnormally resulting in the modification of the cellular proteins pathologic changes in blood vessels, degeneration of the retina, and kidney failure. Untreated diabetes can lead to diabetic coma, death in severe cases. [21]

To treat type 1 diabetes recently, a less intensive immunosuppressive treatment (the Edmonton protocol), coupled with islet cell transplantation into the liver, has produced encouraging responses. [21]

Stem cell based strategies for cell regeneration and Immunomodulation: Obtaining a large source of cells for cellular therapy is a major challenge. Stem cell-based options have a significant therapeutic potential owing to both the intrinsic regenerative capacity and the immunomodulatory potential of stem cells. While the capacity of stem cells to self-renew and to differentiate into specialized cell types can harnessed to make available a self-replenishing supply of glucose-responsive insulin-producing cells for transplantation, the immunomodulatory properties of stem cells, can be used to help arrest cell destruction, facilitate endogenous cell regeneration, and improve islet graft process. Thus, stem cells with immunomodulatory properties can potentially be used, both alone and in combination with cell replacement strategies, to reverse hyperglycemia in Type 1A diabetes mellitus. [22]

3. Cardiovascular disease (CVD):

Cardiovascular diseases (CVD) include hypertension, coronary heart disease, congestive heart failure (CHF), Stroke, etc. It is one of the leading causes for morbidity and mortality in the United States and Europe. [23], [24] CVD may deprive heart tissue of oxygen, thereby killing cardiomyocytes (cardiac muscle cells) which in turn leads to a series of events like formation of scar tissue, an overload of blood flow and pressure capacity, the overstretching of cardiac cells to sustain cardiac output, leading to heart failure, and eventually death. Repairing the damaged heart muscle tissue through regeneration is a potential new strategy to treat heart failure. [23]

<u>Types of stem cells used for Cardiac Transplant:</u>

- Skeletal Myoblasts: The first kind of stem cells used for cardiac therapy was skeletal myoblasts. They are muscle stem cells isolated from muscle biopsies. The first trial took place in 2008 and since then a number of other clinical studies using these stem cells have been initiated for patients who suffer from heart attack or congestive heart failure. [24], [25]

- Embryonic stem cells (ESCs): They are capable of differentiating into cardiac myocytes, but the major issue with their use in human trials is the formation of teratomas. This is particularly important because the ESCs currently available for use in humans would be of allogeneic origin and would require immunosuppression. As nuclear transfer techniques improve, they will provide a way of generating an unlimited supply of histocompatible ES cells using the nuclei of cells obtained directly from the recipients.

- Adult Stem Cells- Bone Marrow–Derived Stem Cells: several preclinical studies show that different types of stem cells can be isolated from adult bone marrow for cardiovascular therapies. Examples include endothelial progenitors and hematopoietic cells. These cells are able to secrete factor that protect the heart and modulate the immune system which is extremely important because these stem cells could be transplanted from one individual to another without the need for the immune suppressing drugs. Endothelial progenitors have a greater potential to promote angiogenesis but are more technically challenging to isolate in significant quantities. Approximately more than 1,000 patients have been transplanted with various types of bone marrow stem cells for heart disease and the outcome has shown to be safe and modestly beneficial. [24], [25]

- Resident Cardiac Stem Cells: Researchers have recently identified a set of stem cells within the myocardium which are capable of differentiating into myocytes. These cells can be harvested from cardiac biopsies. Injecting these cells in the setting of myocardial infarction can promote cardiac muscle formation with associated improvements in systolic function. [24]

4. Parkinson's disease (PD):

Parkinson's disease is a neurodegenerative disease that affects more than 2% of population above 65 years of age. It is caused due to progressive degeneration and loss of dopamine (DA)–producing neurons which lead to tremors, rigidity, hypokinesia. It is thought that PD may be the first disease to be amenable to treatment using stem cell transplant. Researchers when directed mouse embryonic stem cells to differentiate into DA neurons by introducing the gene Nurr 1 and when transplanted into the brains of rat models with PD, these stem cell derived DA neurons the activate brain of the rat models and improved motor function. Similar efforts are being made to make neurotransplantation widely available for Parkinson's patients.

5. Blindness and vision impairment:

Stem cells have proved to be of great importance in the treatment of blindness. Researchers have successfully transplanted corneal stem cells to repair impaired vision in patients. Sheets of

retinal cells were harvested from aborted fetuses and these cells were transplanted over the damaged cornea which eventually restored vision.

Case study: In 2005, doctors in the UK transplanted corneal stem cells from an organ donor to the cornea of a woman who was blinded in one eye following an acid attack. The cornea, which is the transparent window of the eye, is a particularly suitable site for transplants. The absence of blood vessels within the cornea makes this area a relatively easy target for transplantation. In fact, the first successful human transplant was a cornea transplant.

In 2014, researchers demonstrated that stem cells collected as biopsies from human corneas can prevent scar formation without a rejection response in mice with corneal damage. [30], [31]

Regulatory view on stem cells:

Regulatory framework in EU:

The Seventh Framework Program for Research of the European Union, coordinated by the European Medicines Agency, was approved on July 2006 and this Framework provides for funding of research projects with embryonic stem cells in countries where this type of research is legally accepted. There are various guidelines provided like “Guidelines on therapeutic products based on human cells”, “Guidance is also provided about the criteria and tests for all starting materials, manufacturing process design and validation, characterization of cell-base medicinal products, quality control aspects of the development program, traceability and vigilance, and comparison”. The marketing authorization application has been prepared by the European Medicines Agency so that cell therapy products should meet the same administrative and scientific requirements as any other drug. Legislation on cell therapy in Europe is based on three directives:

- Directive 2003/63/EC (amending Directive 2001/83/EC), which defines cell therapy products as clinical products and includes their specific requirements.
- Directive 2001120/EC, which emphasizes that Clinical Trials (CTs) are mandatory for such cell therapy products and describes the special requirements for approval of such trials.
- Directive 2004123/EC, which establishes the standard quality, donation safety, harvesting, tests, processing, preservation, storage, and distribution of human tissues and cells.

The EU regulation (1394/2007) on Advanced Therapy Medicinal Products (A TMPs) became effective from December 2008 it includes gene therapy medicinal products, somatic cell therapy products (as defined in Directive 2001/83/EC), and tissue engineered products

The Committee for Advanced Therapies (CAT) within European Medicines Agency (EMA) is responsible, among other tasks, for preparing a draft opinion on the quality, safety, and efficacy of A TMPs that follow the centralized marketing authorization (MA) procedure. Yet, no MA has been granted for any stem cell based medical product (SCBPM) in the EU. [28], [29]

Regulatory framework in USA:

US federal regulation on cellular therapy is divided into two sections of the Public Health Service Act (PHSA), referred as "361 products" and "351 products" and the traditional blood and bone marrow progenitor cells as well as other tissues for transplantation fall into 361 products definition. The Center for Biologics Evaluation and Research (CBER), the division of US FDA that regulates stem cell based therapies, has so far approved ApliGrat®, Carticel® and Epicel®. Those cell-based therapeutics ''that are, minimally manipulated, labeled or advertised for homologous use only, and not combined with a drug or device" do not require FDA approval. Whereas manipulated autologous cells for structural use meet the definition of somatic cell therapy products and require an "investigational new drug" (IND) exemption or the FDA license approval. Various guidelines provided are: "Guidance for Industry: Regulation of HCT *IPs* - Small Entity Compliance Guide (2007)" and in 2009, the "Guidance for Industry on Current Good Tissue Practice (cGTP) [29]

Regulatory framework in India:

In 2006, Indian Council of Medical Research (ICMR) released "Ethical Guidelines for Biomedical Research on Human subjects" under which Section V gives the requirements for carrying out "stem cell research and therapy". These guidelines have divided research on stem cells into mainly three areas- permissible, restrictive and prohibited areas. Under permissible category, Clinical Trials (CT) with clinical grade stem cells may be carried out with prior approval of Institutional Committee for Stem Cell Research and Therapy (IC-SCRT), Institutional Ethics Committee (IEC) and Drug Controller General of India (DCGI). Clinical and following ICMR Guidelines for Biomedical Research and GCP guidelines of the Government of India (GOI), ICMR and the Department of Biotechnology (DBT) have together laid down "Guidelines for Stem Cell Research and Therapy'' in Nov 2007. This guideline emphasizes on mechanism for review and monitoring research and therapy in the field of human stem cells, on National level (the NAC-SCRT) as well as at the institutional level (the IC-SCRT).

CONCLUSION:

The objectives in the area of stem cell research in the next few years are related to identification of therapeutic targets in the human body depending on the disease.

For instance, bone marrow for leukemia; nerve cells for treating conditions such as Parkinson and Alzheimer diseases; cardiac muscle cells for heart diseases, or pancreatic islets for the treatment of diabetes. Stem cell therapy is one of the ideal means to cure almost all human diseases known, as it would allow for replacing defective or dead cells by normal cells derived from normal or genetically modified human stem cell lines. If such practices are possible in the future, stem cell research will bring about a change in the paradigm of medical practice.

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