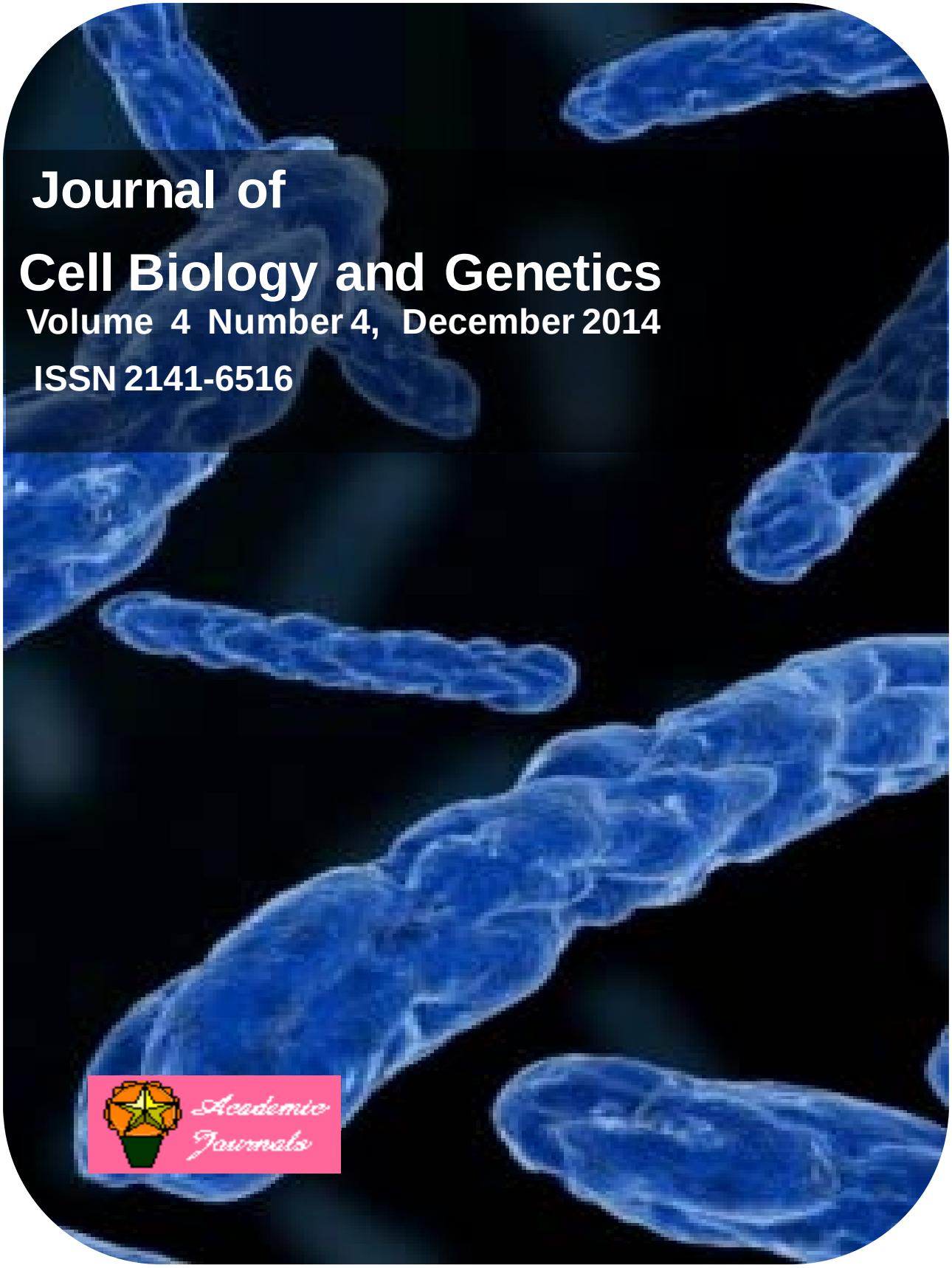

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Journal of Cell Biology and Genetics

Review

Basic biology and therapeutic application of stem cells in various human and animal diseases

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Stem cells are a population of precursor cells that are capable of developing into many different cell types in the body. They are unspecialized cells that can give rise to specialized cells and capable of dividing and renewing themselves for long periods. Based on the potency, stem cells can be totipotent, pluripotent, multipotent, oligopotent, unipotent and based on source it can be divided as embryonic, fetal, adult, amniotic fluid, cord blood, and induced pluripotent stem cells. Stem cell microenvironment (niche) providing support and stimuli to control stem cell properties. The application of stem cells in human medicine is well established and it is commonly used for chronic and accidental injuries and in veterinary medicine they rapidly become a visible tool for regenerative therapy of chronic, debilitating and various unresponsive clinical diseases and disorders. Unquestionably, the development of bioprocess technologies for the transfer of the current laboratory-based practice of stem cell tissue culture to the clinic as therapeutics necessitates the application of engineering principles and practices to achieve control, reproducibility, automation, validation and safety of the process and the product. A stem cell therapy is a treatment that uses stem cells, or cells that come from stem cells, to replace or to repair a patient's cells or tissues that are damaged. Stem cells undoubtedly offer tremendous potential to treat many human and animal diseases and to repair tissue damage resulting from injury. Although stem cell holds pivotal promise in treatments of many incurable diseases, it has many critical limitations.

Key words: Application, biology, bioprocess, limitation, niche, stem cells.

INTRODUCTION

Stem cells are unspecialized cells that can give rise to specialized cells and capable of dividing and renewing themselves for long periods (Arias, 2008). During the last century, efforts toward preventing and battling disease affecting how a cell or a group of cells behave. Unquestionably, this pharmacological approach has

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played, and will continue to play, an invaluable role in efforts to ensure a long and healthy life for humans and animals. It has led to the development of drugs that can combat infection, slow down cancer progression, and help in a myriad of diseases. Yet, even with this large and complex arsenal of drugs, there are many occasions where there were fall short. This has resulted in the search for alternative methods that can be used alone or in combination with pharmacological methods. One of these alternatives focuses on the use of stem cells as the method of treatment (Piedrahita, 2011).

Recent advancement in the field of biotechnology, molecular biology, genetics and immunology has revolutionized biomedical research and therapy in medical and veterinary fields. Sustained efforts have led to the development of many novel therapies and treatment modalities including cytokine therapy, phage therapy (bacteriophages, virophages, mycophages), yolk antibody therapy; herbal therapy and stem cell therapy (Dhama et al., 2013). The subject of stem cell research has attracted tremendous interest of scientists, medical and veterinary professionals in the recent past due to potential application of stem cells in numerous incurable diseases (Gade et al., 2012). Stem cells offer an unprecedented hope in treating many debilitating diseases of humans as well as animals. They have two important distinguishing characteristics, first they are unspecialized cells capable of self-renewal through cell division, sometimes after long periods of inactivity and second under certain physiologic or culture conditions, they can be differentiated to tissue- or organ-specific cells with special functions. Stem cells retain the ability to become some or all of the more than 200 different cell types in the body hence, unique regenerative potential of these cells make their use indispensible in the area of therapeutics. Stem cells are undoubtedly most promising for cell-based therapies that are currently tested in pre-clinical trials for a wide range of ailments for their therapeutic potential. The basic mechanism of action and generalized applications of mesenchymal stem cells were reviewed by various researchers (Spencer et al., 2011). Most of the reports mainly focused on the challenges ahead of clinicians. The current compilation emphasizes on the preclinical and clinical studies of the utilization of embryonic and adult stem cells in laboratory animals, pets and farm animals (Gade et al., 2012).

In recent years, the potential of stem cell research for tissue engineering-based therapies and regenerative medicine clinical applications has become well established. Unquestionably, the development of bioprocess technologies for the transfer of the current laboratory-based practice of stem cell tissue culture to the clinic as therapeutics necessitates the application of engineering principles and practices to achieve control, reproducibility, automation, validation and safety of the process and the product. The successful translation will require contributions from fundamental research (from developmental biology to the 'omics' technologies and advances in immunology) and from existing industrial practice (biologics), especially on automation, quality assurance and regulation (Mark et al., 2009).

Therefore, the objective of this paper is to describe some important points in the area of stem cell biology, bioprocessing and its therapeutic applications in various human and animal diseases.

STEM CELL BASICS

Stem cells and their importance in the body

Stem cells are a population of precursor cells that are capable of developing into many different cell types in the body. When a stem cell divides, each new cell has the potential either to remain a stem cell or differentiate into another type of cell with a more specialized function. Stem cells are distinguished from other cell types in the body by capability of self- renewal and under certain conditions induced to differentiate into specific cells. In some organs, (for example the bone marrow, or skin), stem cells regularly divide to repair and replace worn out tissues which was discovered in the early 1960s, and knowledge about their characteristics and composition has come a long way. The existence of stem cells was first demonstrated in 1960 by Till and McCulloch in a study on hematopoiesis. The establishment of the concept of hematopoietic stem cells (HSCs) was followed by the discovery of tissue stem cells in other organs in mammals, for example, epithelial stem cells, neural stem cells, and intestinal stem cells (Fuchs and Segre, 2000). Stem cells are important for living organisms for many reasons. In the 3 to 5 day old embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all of the many specialized cell types and organs such as the heart, lung, skin, sperm, eggs and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease (http://stemcells.nih.gov/info/stemcellbasics).

The unique properties of all stem cells

Stem cells differ from other kinds of cells in the body. All stem cells regardless of their source have three general properties: Stem cells are unspecialized. One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures and cannot work with its neighbors to pump blood through the body (like a heart muscle cell); it cannot carry molecules of oxygen through the bloodstream (like a red blood cell); and it cannot fire electrochemical signals to other cells that allow the body to move or speak (like a nerve cell).

However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells. Stem cells are capable of dividing and renewing themselves for long periods. When cells replicate themselves many times over it is called proliferation. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal. Stem cells can give rise to specialized cells. When unspecialized stem cells give rise to specialized cells, the process is called differentiation. Scientists are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation. The internal signals are controlled by a cell's genes, which are interspersed across long strands of DNA, and carry coded instructions for all the structures and functions of a cell. The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in the microenvironment. A number of experiments have reported that certain adult stem cell types can differentiate into cell types seen in organs or tissues other than those expected from the cells' predicted lineage (that is, brain stem cells that differentiate into blood cells or blood forming cells that differentiate into cardiac muscle cells and so forth). This reported phenomenon is called transdifferentiation (http://stemcells.nih.gov/info/stemcellbasics).

Types of stem cells

Stem cells can be divided based on their self-renewal and potency (Zhang and Cheng, 2013). Self-renewal is the ability to go through numerous cycles of cell division while maintaining the undifferentiated state while potency is the capacity to differentiate into specialized cell types. Based on the potency, stem cells can be divided into five groups. The first type is the totipotent stem cells. These cells can differentiate into embryonic and extraembryonic cell types. These cells are produced by fusion of an egg and sperm cell. The second type is pluripotent stem cells. These cells are the progenies of totipotent cells and can differentiate into almost all cells except extraembryonic cell types. The cell has the potential to differentiate to any of the three germ layers are examples of this type**.** The third type is the multipotent stem cells which can differentiate into a number of cells, but only those of a closely related family of cells. The fourth type is the oligopotent stem cells. These cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells. Finally, the fifth group is the unipotent cells. Therefore, all types of stem cells have the ability of self-renewal but their potency is different and depends on the source that they have arisen from (Yao et al., 2012). Based on their source, stem cell can also be classified as embryonic, fetal, adult, amniotic cord blood and Induced pluripotent, which are described as follows:

Embryonic stem cells: These cells can be obtained from the epiblast tissue of the inner cell mass of a blastocyst or earlier morula stage of embryos. A blastocyst is an early stage embryo, approximately four to five days old in humans and has about 30 to 160 cells. The embryonic stem cells are pluripotent and give rise to all derivatives of the three primary germ layers that is, ectoderm, endoderm and mesoderm. If a proper stimulation is induced, under an optimum condition, they can be differentiated into more than 200 different cell types of the adult body (Chen, 2012).

Fetal stem cells: The primitive stem cells located in the organs of fetuses are referred as fetal stem cells. Fetal stem cell is one of the best sources for stem cells in veterinary medicine because all fetal tissues are composed of stem cells and without any difficulty these cells can be harvested from the fetus. However, fetal stem cell in human medicine is faced with ethical concerns and for this reason the researches in this area are limited (Guest et al., 2010).

Adult stem cells: Adult or somatic stem cells can be found in children, as well as adults. Pluripotent adult stem cells are rare but can be found in a number of tissues including umbilical cord blood (Uchida et al., 2012). For autogenous adult stem cells, there are three accessible sources:

1. Bone marrow, which requires extraction by harvesting, that is, drilling into bone, typically the femur or iliac crest.
2. Adipose tissue (lipid cells), which requires extraction by liposuction, and
3. Blood, which requires extraction through phrases, where blood is drawn from the donor, similar to a blood donation, passes through a machine that extracts the stem cells and returns other portions of the blood to the donor (Bigham-Sadegh et al., 2012).

Bone marrow has been found to be one of the most reliable sources of adult stem cells which have been used in treating several conditions (Emadedin et al., 2012). The quantity of stem cells of bone marrow has been found to be declining with age. Most adult stem cells are multipotent and are generally referred to by their tissue origin (mesenchymal stem cell (MSCs), adipose-derived stem cells (ADSCs), endothelial stem cell, dental pulp stem cell, etc.). Bone marrow contains two main cell types: hematopoietic cells and stromal cells. The stem cells for non-hematopoietic tissues are referred as MSCs because of their ability to differentiate as mesenchymal or stromal cells. The mesenchymal cells are easily obtainable from bone marrow by means of minimally invasive approach and can be expanded in culture and permitted

to differentiate into the desired lineage (Obermeyer et al., 2012).

Amniotic derived stem cells: Multipotent stem cells are also found in amniotic fluid. These stem cells are very active, expand extensively without feeders and are not tumorigenic. Amniotic stem cells can differentiate into adipogenic, osteogenic, myogenic, endothelial, hepatic and also neuronal cell lines. Application of stem cells from amniotic fluid overcomes the ethical objections of using human embryos as sources of cells. It is possible to collect amniotic stem cells for donors or for autologous use (Uchida et al., 2012).

Cord blood derived stem cells: Recently, new source has been introduced for the autogenous stem cells. In fact, stem cells can be obtained from umbilical cord blood just after birth. A certain kind of cord blood stem cell is multipotent and displays embryonic and hematopoietic characteristics. Cord blood stem cell display very low immunogenicity because of expressing very low level of major histocompatibility complex antigens and failure to stimulate proliferation of allogeneic lymphocytes. They can give rise to three embryonic layer-derived cells in the presence of different inducers (Emadedin et al., 2012).

Induced pluripotent stem cells (iPSs): Scientists have recently found another way of producing pluripotent stem cells without using embryos. In 2006 to 2007, scientists discovered how to 'reprogramme' some specialised cells to become pluripotent so that they lose their specialist functions and behave in virtually the same way as embryonic stem cells. The starting cells are reprogrammed into a pluripotent stem cell state. Pluripotent cells generated in this way are called induced pluripotent stem cells (iPS cells). iPS cells were first produced in mice, and it was quickly shown that the same method could be used to make human iPS cells. Scientists can make iPS cells using any kind of cell in the body, but most often skin cells are used as they are easy to obtain. These are not adult stem cells, but rather adult cells (example, epithelial cells) reprogrammed to give rise to pluripotent capabilities. Using genetic reprogramming with protein transcription factors, the pluripotent stem cells equivalent to embryonic stem cells have been derived from human adult skin tissue (Gulotta et al., 2011). There were three major streams that led to the production of iPSCs: The first stream was reprogramming by nuclear transfer; the second stream was the discovery of ''master'' transcription factors; the third, and equally important, stream of research is that involving embryonic stem cells (ESCs). Combining the first two streams of research led to hypothesize that it is a combination of multiple factors in oocytes or ESCs that reprogram somatic cells back into the embryonic state and to design experiments to identify that combination. Using information about the culture conditions that are needed to culture pluripotent cells were then able to identify four factors that can generate iPSCs (Yamanaka and Blau, 2010).

Stem cell niche

In 1978, Schofield proposed the "niche" hypothesis to describe the physiologically limited microenvironment that supports stem cells (Schofield, 1978). In recent years, newer mechanisms like niches or special tissue microenvironment have been studied well that has helped to understand the mechanism of regulation of stem cell. Candidate niches as well as regulatory molecules in several mammalian tissue viz., bone marrow and skin; gut and brain have been identified (Gokhale and Andrews, 2008). Many common features, structures, and functions of the stem cell niche have been found after comparison of the stem cell niches in the ovary and testis of *Drosophila* and in *Caenorhabditis elegans,* as well as in mammalian bone marrow, hair follicle, intestine, brain, and testis, and are summarized as follows (Linheng and Ting, 2005).

1. The stem cell niche is composed of a group of cells in a special tissue location for the maintenance of stem cells. The niche's overall structure is variable, and different cell types can provide the niche environment. For example, N-cadherin-positive osteoblastic lining cells in the trabecular bone form the niche for hematopoietic stem cell (HSCs), whereas endothelial cells form the NSC cell niche.
2. The niche functions as a physical anchor for stem cells. E-cadherin-mediated cell adhesion is required for anchoring germ line stem cells and somatic stem cells in Drosophila, and Ncadherin may be important for anchoring HSC in the bone marrow niche. Other adhesion molecules, such as integrins, may help anchor stem cells to extracellular matrixes.
3. The niche generates extrinsic factors that control stem cell fate and number. Many signal molecules have been shown to be involved in regulation of stem cell behavior, including hedgehog, wnts, bone morphogenesis proteins, fibroblast growth factors, notch, stem cell factor, angiotension-1, and leukemia inhibitory factor or unpaired through the JAK-Stat pathway. Several pathways can be utilized to control self renewal of one stem cell type, whereas one growth factor can regulate several different stem cell types. The presence of signaling components of multiple conserved developmental regulatory pathways in stem cells supports the ideas that stem cells retain the ability to respond to these embryonic regulatory signals and that orchestration of these signals is essential for proper regulation of stem cell self-renewal and lineage commitment.
4. In invertebrates and mammals, the stem cell niche exhibits an asymmetric structure. Upon division, one daughter cell is maintained in the niche as a stem cell

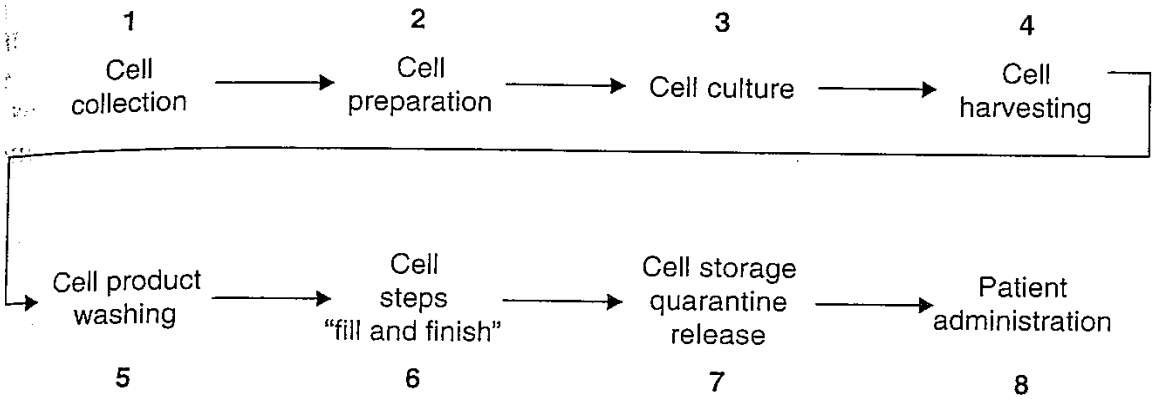

Figure 1. Cell production steps for ex vivo cell therapy.

(self-renewal); the other daughter cell leaves the niche to proliferate and differentiate, eventually becoming a functionally mature cell.

Stem cell bioprocessing: Fundamentals and principles

The success of stem cell bioprocessing relies on robust and reproducible culture conditions and processes. For stem cell bioprocessing, this includes the scale-up of stem cells to a differentiated end product of sufficient quality and quantity for clinical and commercial goals. Automation and the use of an efficient bioprocess paradigm are imperative for the creation of successful clinical products. The design principles (Lim et al., 2007) pertinent to stem cell bioprocessing can be categorized into three groups: process components; process requirements and process function, as summarized in Figure 1. A combination of generic, 'off-the-shelf' and personalized manufacturing paradigms must be considered as no single technology satisfies all requirements (Mark et al., 2009). (Figure 2)

Process components

Identification of the optimal cell source and important signals for cellular development, as well as delivering suitable growth mimicry in terms of the scaffold used, are essential tailor-made requirements in stem cell bioprocessing and tissue engineering. In addition, provision of a controlled culture environment through the use of an appropriate bioreactor is critical (Lim et al., 2007).

Stem cells: There are several classes of stem cells, each one presenting its own challenges and benefits for the manufacture of therapeutics for the clinic. An important consideration with respect to bioprocessing is the expansion potential of these cells. ESCs are believed to have an almost unlimited expansion capability while adult stem cells, depending on donor and source, may be capable of only tens of population doublings. In general, a firm correlation exists between the expansion and/or differentiation ability and availability of the stem cells and their clinical applicability in terms of process complexity, and ethical and regulatory restrictions. Clearly different stem cell types will require different operating conditions; however, this variability is also likely in any one stem cell type from initial expansion to differentiation. Finally, stem cell standardization necessitates the identification of appropriate markers as well as the development of suitable evaluation assays (Mark et al., 2009).

Operating conditions and signals: Successful stem cell bioprocessing, in terms of expansion and differentiation, depends on the control of key process variables: the physiochemical environment; nutrients and metabolites and growth factors. Physiochemical culture parameters include pH, dissolved oxygen and carbon dioxide tensions and temperature. Oxygen tension is a critical factor in haemopoiesis. In culture, oxygen tension can greatly affect the expansion of cells by modulating the production of cytokines, surface markers and transcription factors (Mostafa et al., 2001). Fewer investigations have been conducted on the effects of temperature, though in most haemopoietic cell cultures, the operating temperature is maintained at 37°C. Process variations in the culture environment could be strategically applied to direct and manipulate cellular behavior in vitro. Nutrient and metabolite concentrations determine cell growth, differentiation and death in a culture, and therefore should be closely monitored and controlled in bioprocessing. Growth factors regulate stem cell behavior by providing survival, proliferation and differentiation signals to the cells. They have specific functions, both positive and negative in nature, and can act on either a specific cell lineage or multiple lineages. Interactions between these growth factors and/or with other process parameters are in many cases not fully understood. It is therefore, crucial to

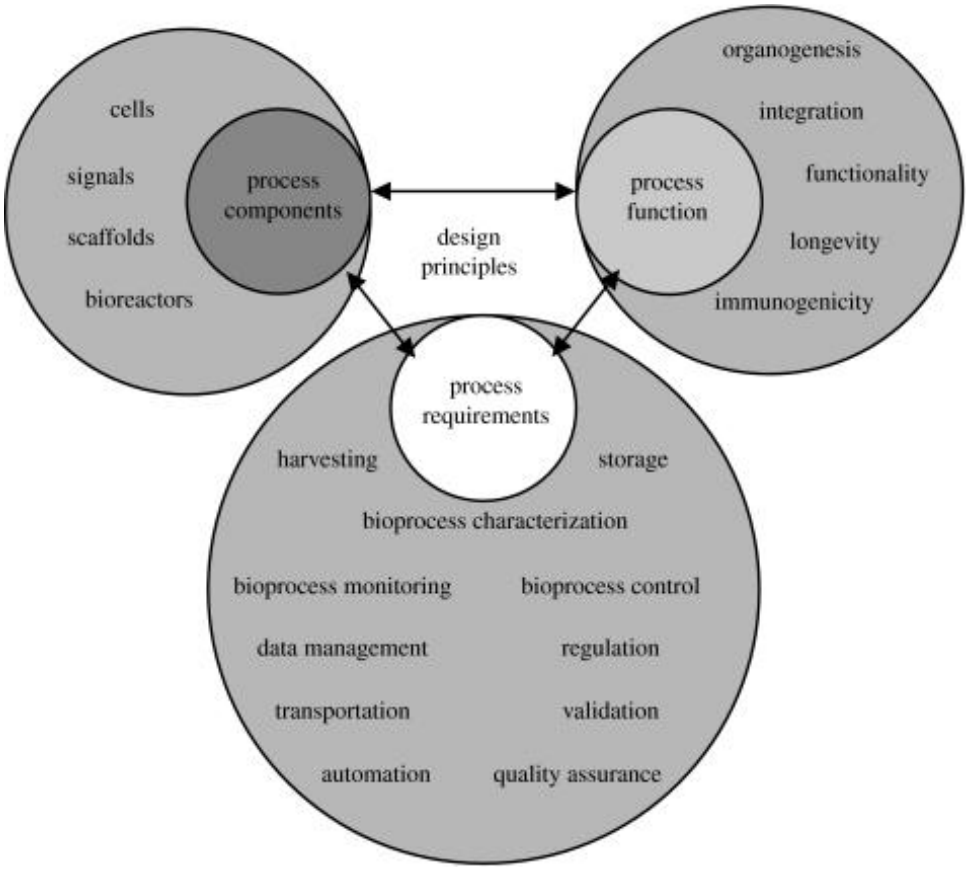

Figure 2. Design principles for stem cell bioprocesses. Source: (Lim et al., 2007).

quantify and qualify these effects and their interactions with respect to one another in order to tailor the culture process for optimal production of a specific cell type population (Lim et al., 2007).

Cell adhesion and scaffolds: Organogenesis, which involves the finely regulated proliferation and differentiation of stem cells, depends, to a large extent, on cell adhesion and the provision of a three-dimensional growth environment. Cell adhesion to the extracellular matrix (ECM) is mediated by a class of heterodimeric transmembrane cell surface receptors called integrins. ECM proteins typically affect cell behavior by binding to specific integrin cell surface receptors, thus activating intracellular signalling pathways that control gene expression, cytoskeletal organization and cell morphology. Furthermore, the signal-transducing capacity of integrins has been indicated as a likely regulator of the in vitro differentiation of several types of stem cells and committed progenitor cells (Hayashi et al., 2007). Consequently, differentiation of stem and progenitor cells can be manipulated through the modification of cell culture surfaces. Indeed, numerous studies have shown that the modulation of cell adhesion properties via surface chemistry, surface microarchitecture or the types of ECM ligands present on the culturing surfaces could be applied to regulate stem cell differentiation (Sun et al., 2006). The use of three-dimensional scaffolds has been explored and needs to be taken into consideration. Designing a tissue-engineered scaffold requires the consideration of a large number of variables: material; porosity; pore size; mechanical stability; degradability; biocompatibility; hydrophobicity; bioactivity. Scaffolds are typically fabricated by either natural or synthetic materials (Safinia et al., 2006) that will facilitate cellular growth and organogenesis in a biomimetic manner (Stevens and George, 2005).

Bioreactors: Stem cell bioprocessing involve the use of specialized devices called bioreactors that aim to facilitate mass transport, high cell density, monitoring and feedback and tissue-specific functional specialization, thus mimicking the ultimate bioreactors, which are the tissues/organs within the human body. An optimal and universal system for stem cell culture does not exist; however, bioreactor development throughout the last 40 years has advanced the technology considerably. The potential of bioreactors to address culture of stem cell from small to large numbers required for clinical therapies is demonstrated by their capacity to support high cell

densities in relatively small volumes, while the scaling up of the design, given mass transfer limitations, will depend on the type of bioreactor chosen. Three-dimensional culture systems that would closely resemble the in vivo conditions by accounting for the cell–cell, cell–matrix and cell–growth factor interactions are required in many clinically relevant cases (Mantalaris et al., 2004). Primarily, perfusion and stirring have been the main means for enhancing mass transport. Stirred suspension bioreactors require careful impeller design to avoid high shear stress that can damage the cells (Zandstra et al., 1994), can be operated either in batch or continuous mode, and result in at least a 10-fold increase in cell density compared with the traditional methods. As already mentioned, the diversity of stem cell sources and their respective culture conditions means that no one bioreactor system is suitable for all stem cells. Therefore, a comparison of bioreactor suitability for their expansion and associated cost is somewhat futile. However, with respect to industry and commercialization, cost is a consideration of great importance. The optimal bioreactors achieve production not by embracing traditional scale-up principles (larger bioreactors) but through process intensification, modularity, specialization and integration. The use of bioreactors is critical for tissue engineering and regenerative medicine applications for control, scale-up, automation and regulatory reasons (Lim et al., 2007).

Process requirements

Ultimately, the integration of the various process components will be required in order to achieve a clinically relevant product through a regulated and controlled bioprocess that is reproducible, standardized, automatable (when needed), integrated and certified. Furthermore, process requirements will also be, by the nature of the problem, application specific (Mark et al., 2009).

Bioprocess monitoring and quality control: Stem cell culture complexity, heterogeneity of cell types and the inherent variability in process performance over time and between batches render the control in bioprocess culture systems a tremendously challenging task (Lim et al. 2007). However, bioprocess control in the manufacturing of biopharmaceutical products is critical in maintaining high product quality and consistency. Efforts are continuously being made in this area to improve process monitoring and control techniques in complex bioprocesses. Specifically, the 'Process Analytical Technology' initiative was established to promote better understanding and control of manufacturing bioprocesses through the use of process and end point monitoring tools, process control tools, multivariate data acquisition and analysis tools, process analytical chemistry tools and knowledge management tools (Junker and Wang, 2006). Integration of various engineering tools is therefore necessary to achieve these goals. With advances in sensor, optical and computer technology, stronger emphasis is being placed on the integration of online, real time, in situ monitoring systems (Clementschitsch and Bayer, 2006).

Product/process characterization proteomic and genomic analyses: Genomic technologies, such as microarray chromatin immunoprecipitation and chromatin immunoprecipitation sequencing, allow for the total characterization of transcription factors and other DNA-bound proteins in a high-throughput and cost-effective fashion. Comparative genomic hybridization can determine total genomic chromosomal losses or gain with respect to a control and test genome. Such technologies are powerful tools to help elucidate the molecular mechanisms that regulate the formation, self-renewal and differentiation of stem cells and also used to determine the effect of drugs and growth factors on cells they are exposed to (Yu et al., 2007). Similarly, proteomics is a tremendously important tool allowing proteome mapping, differential analyses and elucidation of signals and mechanisms, thus enabling the understanding of the complex biological processes and protein-regulated signalling pathways that constitute basic embryonic development and stem cell differentiation. Proteomics has facilitated the elucidation of the complex environment provided by feeder cells leading to the development of feeder-free, defined culture conditions, which are essential for the clinical applications of cellular products. Furthermore, proteomics is a powerful differential analysis technique. Proteomics can also be used to characterize an environment that supports maintenance of undifferentiated stem cells and to help identify factors critical for their differentiation (Sze et al., 2007).

Regulation: The clinical application of stem cell products will require the whole process of cell separation, manipulation, culture, characterization, storage and delivery to be tightly controlled and satisfy strict regulatory requirements. The Food and Drug Administration (FDA) in the United State of America has divided cell therapies into two groups, commonly referred to as '361 products' and '351 products'. Traditional blood and bone marrow progenitor cell products as well as some tissues for transplantation are usually considered 361 products. Cells that are more than minimally manipulated or intended as a drug are considered 351 products. The 361 products typically have short processing times and require closed systems under 'Good tissue practices', whereas 351 products must be manufactured according to Current 'Good manufacturing practices' in addition to the 'Good tissue practices' requirements. As most cell therapy protocols fall within the 351 products category, 'Good manufacturing practices' facilities need to be taken into consideration when developing a cell therapy programme (Dietz et al., 2007; Mark et al., 2009).

Therapeutic application of stem cell in human and animal diseases

Research in stem cell field can enormously help the field of agriculture as well as biomedical, veterinary and pharmaceutical research (Brown et al., 2012; Gade et al., 2012). Although, stem cells are primarily important in area of regenerative medicine in the treatment of several incurable ailments, it were applicable in many scientific studies such as, in understanding of cancer biology (Ricardo et al., 2003), genomic fingerprinting and development of the embryo at an early stage, application in drug screening and tissue engineering (Gurtner et al., 2007), helpful in generating transgenic animals (Brevini et al., 2008) and animal biotechnology (West et al., 2010), testis xenografting and spermatogonial stem cell transplantation (Lisa and Alexander, 2011).

A stem cell therapy is a treatment that uses stem cells, or cells that come from stem cells, to replace or to repair a patient's cells or tissues that are damaged. The stem cells might be put into the blood, or transplanted into the damaged tissue directly or even recruited from the patient's own tissues for self-repair. Local delivery or systemic infusion may be required for the transplantation of autologous or allogeneic stem cells into patients for stem cell therapy. Stem cells undoubtedly offer tremendous potential to treat many human and animal diseases and to repair tissue damage resulting from injury or ageing (Lau et al., 2008). The most standard methods of stem cell therapy are direct injection or cell seeding (cell + scaffold) and transplantation of a graft. The general principle of stem cell therapy is to exploit the natural ability of the human and animal body to heal tissues through the process of regeneration. It may be possible to use stem cell therapies to combat major diseases such as heart disease, bone or connective tissue disorders, neural defects, and hematological disorders (Despoina et al., 2008). At least three types of therapeutic strategies are considered when using stem cells. The first is stimulation of endogenous stem cells using growth factors, cytokines, and second messengers, which are able to induce self-repair of damaged tissues or organs. The second alternative is direct administration of stem cells so that they can differentiate the damaged or non-functional tissue sites. The third possibility is transplantation of cells, tissues, or organs taken from cultures of stem cell-derived differentiated cells. The United State Food and Drug Administration defines somatic cell therapy as the administration of autologous, allogeneic, or xenogeneic non-germ cells–excluding blood products for transfusion–which have been manipulated or processed and propagated, expanded, selected ex vivo, or drug-treated (Liras, 2010).

Most common human disease treated with stem cells

Neurodegenerative diseases hold an opportunity for the clinical use of stem cells. In neuroscience, the discovery of neural stem cells (NSCs) and subsequent research have nullified the previous idea that the adult central nerve system was not capable of neurogenesis. Indeed, neurogenesis occurs throughout life. NSCs are believed to reside within the subventricular zone of the lateral ventricle wall and the subgranular zone of the hippocampal dentate gyrus, where neurogenesis occurs (Zhao et al., 2008). (Figure 3)

Alzheimer's disease (AD) is characterized by neuronal and synaptic loss throughout the brain, involving the basal forebrain cholinergic system, amygdala, hippocampus and several cortical areas. Current therapies, such as treatment with acetyl cholinesterase inhibitors to enhance cholinergic function, provide only partial and temporary alleviation of symptoms. The pathological changes seen in AD offer an extremely problematic situation for cell replacement. The data show that neural stem cells release diffusible factors that may improve the survival of aged and degenerating neurons in human brains (Zhongling et al., 2009). Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and a reduction in striatal dopamine. In PD, the loss of dopaminergic neurons in the substantia nigra pars compacta leads to impaired information processing in the basal ganglia. The main symptoms are rigidity, poor movement, tremors and postural instability. Although the pharmacological treatment is effective for some symptoms, it has some limitations because its effectiveness decreases over time and side effects develop (Prokai et al., 2008). Thus, an alternative approach for restoration of the damaged dopaminergic system is transplantation of dopaminergic -synthesizing cells. Human stem cells may provide sources of cells for use in the treatment of PD (Zhao et al., 2008).

Leukemia is one of the life threatening diseases in human life. The Leukemia's are neoplastic disorder of hemopoitic tissue where an uncontrolled, abnormal and wide spread proliferation of the leucocytic cells (white blood cells) occurred. Every year a huge number of people around the world are attacked by these diseases. A common treatment for these diseases is chemotherapy. But it has some problem also. At first most growing cells like leukemia or neoplastic cells are destroyed by the cytotoxic agents, due to chemotherapy. These agents also kill the hematopoietic stem cells within the bone marrow. Unfortunately this side effect arises a question about the use of the chemotherapy. To solve this problem scientists use stem cell as a therapeutic purposes. For over many years bone marrow stem cells have been used by the scientists to treat patients with leukemia and lymphoma (University Hospitals of Cleveland, 2004). A major hurdle facing nephrology researchers is that the human kidney has been classically defined as a non-proliferative and non-regenerative organ. However, with the discovery of adult stem cells in organs that were once thought to be non-regenerative, the cellular make-up of

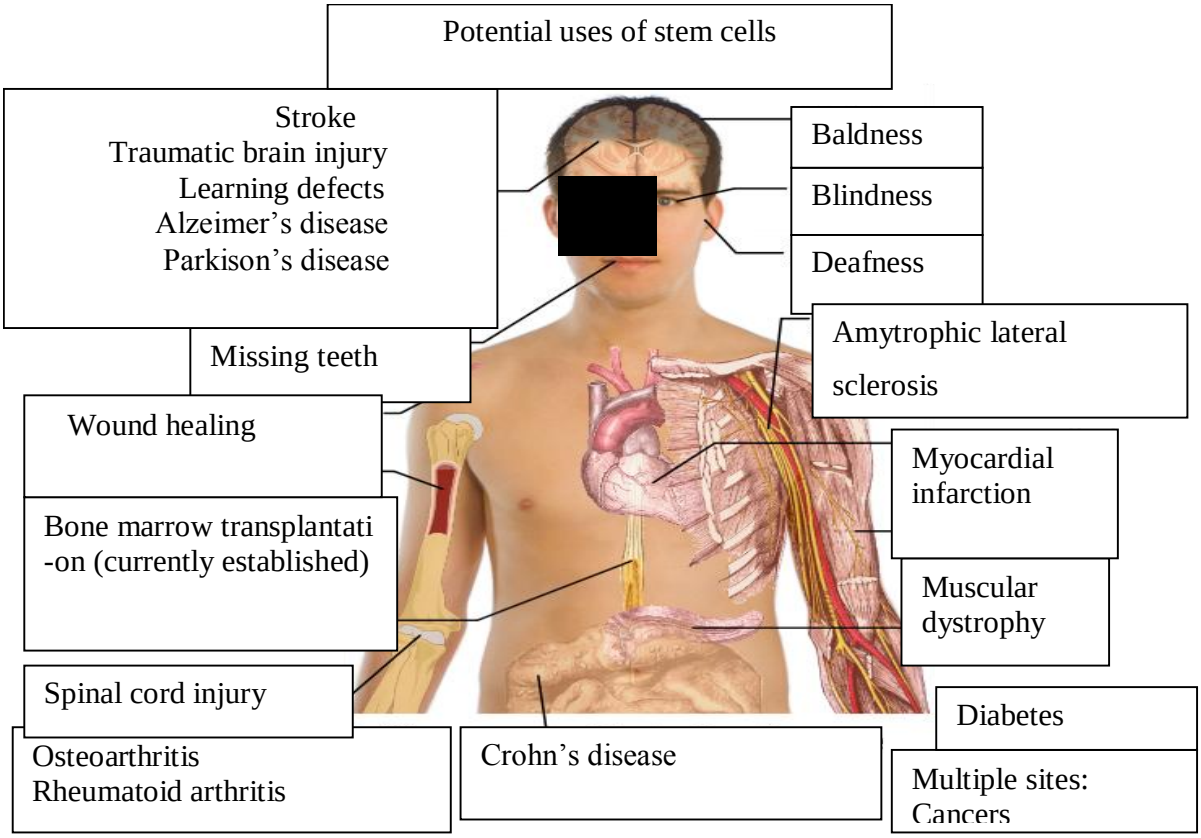

Figure 3. Human disease treated with stem cells. Source: http://www.stemcell.net.in/stemcelltreatment

the kidney has come to be reevaluated. There is emerging evidence that human kidneys possess innate regenerative abilities (Yue and Rebecca, 2013).

Type 1 diabetes, also called juvenile diabetes, is an autoimmune disease that frequently presents itself from infancy to the late 30s. It results from the body's failure to produce insulin, a hormone that signals the body to allow glucose to enter cells and fuel them. The fundamental cause of type 1 diabetes is the absence of a single kind of cell, the pancreatic beta islet cell (beta cell). For unknown reasons, the immune system sometimes launches an attack against the body's own insulin-producing beta cells and destroys them. The current treatment for type 1 diabetes calls for injections of insulin to control blood glucose, requires constant vigilance and affords only imperfect glucose control, the long-term potential consequences of which are cardiovascular disease, blindness, kidney failure and damage to the peripheral nervous system. Generation of insulin-secreting cells from human ESCs held important promise strategy for the treatment of diabetes, a disease of increasing prevalence worldwide (Pai-Jiun et al., 2012). Other stem cells therapeutic applications, still in their first steps, include treatment of hereditary monogenic diseases such as hemophilia using hepatic sinusoidal endothelial cells or murine iPSCs obtained by fibroblast differentiation into endothelial cells or their precursors (Xu, et al., 2009). As regards hemophilia, an optimum candidate because it is a monogenic disease and requires low to moderate expression levels of the deficient coagulation factor to achieve a moderate phenotype of disease, great progress is being made in both gene therapy and cell therapy using viral and non-viral vectors (Liras, 2001).

Current pharmacologic interventions for heart disease, including beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors, and surgical treatment options, such as changing the shape of the left ventricle and implanting assistive devices such as pacemakers or defibrillators, do not restore function to damaged tissue. Although heart transplantation offers a viable option to replace damaged myocardium in selected individuals, organ availability and transplant rejection complications limit the widespread practical use of this approach. These have led researchers to explore the application of embryonic and adult-derived stem cells for cardiac repair. A number of stem cell types, including embryonic stem cells, cardiac stem cells that naturally reside within the heart, myoblasts (muscle stem cells), adult bone marrow-derived cells, mesenchymal cells, endothelial progenitor

cells, and umbilical cord blood cells, have been investigated to varying extents as possible sources for regenerating damaged myocardium (Jackson et al., 2001).

Stem cell therapy has been demonstrated to induce profound healing activity in animals with various forms of autoimmune disorders (rheumatoid arthritis, multiple sclerosis, and lupus). Besides healing damaged tissues, stem cells have the unique ability to modulate the immune system so as to shut off pathological responses while preserving its ability to fight off disease. Stem cells and specifically, mesenchymal stem cells home to inflamed tissue and start producing anti-inflammatory agents. These mediators act locally and do not suppress the immune response of the patient's whole body. Additionally, mesenchymal stem cells induce the production of T regulatory cells, a type of immune cell whose function is to protect the body against immunological self attack (https://www.cellmedicine.com/stem-cell-therapy-for-autoimmune-diseases/).

Therapeutic application of stem cells in veterinary medicine

The stem cell field in veterinary medicine continues to evolve rapidly both experimentally and clinically. At present, stem cell therapies in veterinary patients are not rigorously supervised by regulatory agencies in any country (Yingling and Nobert, 2008). Unfortunately, this has led to the implementation of some therapies that have not demonstrated efficacy *in vitro* or in preclinical animal studies. The therapeutic application of stem cell-based technologies in veterinary medicine was first used by Herthel to treat equine suspensory ligament desmitis (Herthel et al., 2002).

Stem cells are most commonly used in clinical veterinary medicine in therapeutic applications for the treatment of musculoskeletal injuries in horses and dogs. Most stem cells intended for regenerative therapy are generally isolated either from the patient's bone marrow or from adipose tissue. MSCs can differentiate into bnb bthe cells that make up bone, cartilage, tendons, and ligaments, as well as muscle, neural and other progenitor tissues; they have been the main type of stem cells studied in the treatment of diseases affecting these tissues. Embryonic stem (ES) cells, induced pluripotent stem (iPS) cells, and cord blood-derived cells are also beginning to be investigated in the laboratory but have not yet been applied to the clinical scenario. Companion animals can serve as clinically relevant models that closely mimic human disease (Pittenger et al., 1999). Osteoarthritis is the main cause of joint pain both in animals and humans. Horses and dogs are most frequently affected arthritis. Natural cartilage regeneration is very limited and no current drug therapies are curative, but rather look to reduce the symptoms associated with the degeneration. Different types of MSCs and other additives are still being researched to find the best type of cell and method for long term treatment. ADMCSs are currently the most often used because of the non-invasive harvesting. There has been a lot of success recently injecting MSCs directly into the joint. This is a recently developed, non-invasive technique developed for easier clinical use. Dogs receiving this treatment showed greater flexibility in their joints and less pain (Ribitsch et al., 2010).

Bone has a unique and well documented natural healing process that normally is sufficient to repair fractures and other common injuries. Misaligned breaks due to severe trauma, as well as things like tumor resections of bone cancer, are prone to improper healing if left to the natural process alone. Scaffolds composed of natural and artificial components are seeded with MSCs and placed in the defect and then newly formed bone begins to integrate with the old bone within four weeks and within 32 weeks, full union is achieved (Guercio et al., 2012). Spinal cord injuries are one of the most common traumas brought into veterinary hospitals. Spinal injuries occur in two ways after the trauma: the primary mechanical damage, and in secondary processes, like inflammation and scar formation, in the days following the trauma. These cells involved in the secondary damage response secrete factors that promote scar formation and inhibit cellular regeneration. MSCs that are induced to a neural cell fate are loaded on to a porous scaffold and are then implanted at the site of injury. The cells and scaffold secrete factors that counteract those secreted by scar forming cells and promote neural regeneration (Hak-Hyun et al., 2009).

Tendon lesions are a major cause of lameness and reduced performance in athletic horses and may result in the early termination of the animals' careers. Tendinous structures are poorly vascularized, are relatively acellular, and have limited potential for regeneration because the tendon repair is prolonged and results in the formation of scar tissue, which is biomechanically inferior and prone to lesion recurrence. Various therapies for tendonitis have been described; however, none of these therapies results in complete tissue regeneration, and the injury recurrence rate is high even after long recovery periods involving rest and physiotherapy. Regenerative medicine has significantly evolved; the uses of mesenchymal stem cells (MSCs) in the therapy of equine tendonitis have shown good results (Carvalho et al., 2013).

Suspensory ligament injuries are a common problem in horses that can result in performance-limiting lameness. Many times, ligament injuries heal slowly and are weaker than before an injury due to scar tissue that forms in the area of the injury. This scar tissue is never as strong or as elastic as the original tissue, which puts this area at higher risk for re-injury. Over the years, veterinarians have used many methods to help horses with ligament injuries, but the success rate remains low, particularly in

hind limb suspensory injuries. Injection of stem cells from a horse's bone marrow into the injured area of the proximal suspensory ligament provides good responses. Though not proven yet, bone marrow stem cells are thought to stimulate natural ligament regeneration that should more closely resemble the original tissue (WSU, 2009).

Limitation of stem cell therapy

There are many ethical debates raised from the use of oocytes and blastocyst and their donation. All policies prohibit payment in exchange for oocyte or blastocyst donation for research purposes and the idea of buying or selling blastocysts is similar to the idea of buying and selling children. There is a very strong opposition to the destruction of human embryos by different groups in society. Some people maintain that human embryos deserve the same respect as any other human being. A blastocyst is not an ordinary cluster of cells. It contains a complete set of genetic instructions and the capacity for the epigenetic determinations needed to develop into a viable human being. Therefore, it is argued that respect for human beings must be the same, regardless of the developmental stage in which the given human individual now stands (Miguel, 2002).

The usefulness of stem cell therapy is restricted by the body's rejection of cells and tissues. Structures present on cell surfaces cause the cells to be rejected when transplanted into another body. The use of stem cells in cell and tissue transplantations thus requires donor and recipient tissues to be compatible. The therapeutic use of stem cells is also restricted by the fact that their differentiation is somewhat unpredictable. Stem cells have the ability to divide indefinitely, a characteristic they share with cancer cells. The fear of uncontrolled growth and cancer limits the use of stem cells, especially embryonic stem cell for their potential to teratoma formation (Zhili et al., 2014).

A major difficulty that scientists continue to encounter is the identification of stem cells in adult tissues. These tissues contain many different types of cells and an attempt to locate the often scarce numbers of stem cells in tissues that could contain thousands of different cells is difficult at best. The research involved is complex and even after cells are isolated, the process to successfully trigger differentiation into the desired cell type is another challenge for researchers. This requires an understanding of stem cell control and regulation that has yet to be not fully gained. In addition, researchers must also use the correct laboratory medium, or solution, to coax the growth and this has proven to be difficult. If scientists do manage to identify, isolate and trigger the appropriate differentiate of stem cells, the cells still must be implanted into the patient and accepted among the native body cells. This success is therefore dependent on effective integration into the patient's body systems and other cells. For example, if cardiac cells are implanted, they must be able to beat in sync with the patient's own heart cells. For a patient who suffers from a neural based disease, any neural cells must integrate into the complicated network of natural neural cells if they are to effectively function and replace damaged cells (http://www.explorestemcells.co.uk/ChallengesOfStemCellTherapy.html).

The cost of stem cell therapy is extremely expensive. The high cost of stem cell therapy is certainly beyond the financial ability of ordinary citizens. Even with subsidization from the Government, the cost of stem cell therapy is still far beyond normal affordability. With the extremely high cost of stem cell therapy in the medical industry, many patients remain to be untreated. This is a cruel reality of medical costs in virtually every country in the world especially in poor country. Though the potential of stem cell therapy sounds promising, the high price tag takes away all hope for ordinary people with incurable diseases. (Figure 4)

CONCLUSION AND RECOMMENDATIONS

The science of stem cells is a field with great potential for treating injury and disease. Stem cells are undoubtedly, most promising for cell-based therapies thereby provides a powerful and flexible option for physician and veterinarians to restore function and improve human and animal health through the novel techniques. The capability of stem cells to self-replicate and to differentiate into a specific, more specialised cell type is what makes stem cells so promising in the treatment of specific diseases. Research in field of stem cells can also enormously help the field of agriculture as well as biomedical, veterinary and pharmaceutical researches. In recent years, the potential of stem cell research for tissue engineering-based therapies and regenerative medicine clinical applications has become well established.

The success of stem cell bioprocessing relies on robust and reproducible culture conditions and processes. Neurodegenerative diseases, leukemia, kidney disease, type 1 diabetes, heart diseases, autoimmune disorders hold an opportunity for the clinical use of stem cells in human medicine. Stem cell therapy in regenerative veterinary medicine is a viable option for the equine as well as the small animal veterinarian, offering a safe and clinically effective tool for the clinician to assist in his/ her treatment of the animal with difficult wounds or unresolved musculoskeletal or joint pain whereas research is still going on in other farm animals. The modern vets-scientist team efforts will play a pivotal role in the development and implementation of these innovative strategies to ultimately improve livestock production and pet care. There are ethical, technical, fundamental scientific issues that are believed to hamper the progress of applied stem cell research and therapeutic applications

Figure 4. Challenges of stem cell therapy. Source: **(**http://www.polyclonebio.com/newsletter/Issue1Articles/Challenges/)

considerably. Based on the above conclusion the following recommendation is forwarded:

1. Sufficient preclinical studies should develop in relevant small and large animal models to make proposed stem cell-based clinical research ethical.
2. Cells to be employed in clinical trials must first be rigorously characterized to assess potential toxicities through *in vitro* studies and in animal studies.
3. All studies involving the use of non-human primates must be conducted under the close supervision of qualified veterinary personnel with expertise in their care and their unique environmental needs.
4. To facilitate international collaboration and universal access to stem cell-based treatments, there is a need to develop appropriate quality management systems for donation, procurement, testing, coding, processing, preservation of stem cell potency, storage, and distribution of the cells.

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