TITLE: STEM CELL THERAPY

AMAN KUMAR, ARCHI BINDRA, DR.A.N SAHI

Student, Amity Institute of Biotechnology, Amity University, Uttar Pradesh, India
Student, Amity Institute of Biotechnology, Amity University, Uttar Pradesh, India
Professor, Amity Institute of Biotechnology, Amity University, Uttar Pradesh, India

Abstract

Variable potency is found in stem cells. It is possible for cells within the human body to self-renew and develop into a wide variety of cell types. Various differentiated cells can be formed from these undifferentiated cells. These cells can be distinguishable from the other cells of the body as they possess the unique property that they can self-regenerate and divide and transform to form the specialized cells. They are o two kinds: embryonic and adult ST cells. Embryonic ST cells initiate the process of human development, whereas adult ST cells replace damaged tissues in fully grown individuals. 2007 brought the discovery of induced pluripotent ST cells (iPS cells). Similar to embryonic cells, these iPS cells have the potential to create all organ systems. It can be said that iPS cells have the benefit of being cultured in vitro to form and are not associated with ethical issues. A number of research developments have resulted in recent years since iPS cells have provided a great deal of potential to treat various diseases. Hence, these cells are crucial to the future of regenerative medicine. Regenerative medicine is the latest, novel, and contemporary field of clinical science. Using specialized cells, cells located in damaged tissues or organs and afflicted by chronic disease can be restored to their original function. Thanks to the amazing advances in this research field, cell therapy and treatments have been developed for diseases that were not cured by traditional medicine. In regenerative medicine, ST cells are the frontiers of self-renewal and reconstruction. Study discusses recent developments and progress in regenerative medicine for transplantation and for tissue engineering for a variety of ST cells.

Keyboard: *Stem cell, Stem cell therapy, regenerative medicine*

Review of Literature:

With the help of StemcellDB (Database for stem cells), we studied the literature to track down relevant data and research ways in which ST cells can benefit regenerative medicine, as this therapy has long been considered a promising and advanced field of science. Studying the identification and potential uses of them is the focus of this review. The analysis is summed up by obstacles that this therapy must resolve in order to be adopted internationally. A broad variety of options makes this leading edge treatment a turning point in medical medicine, offering hope for diseases which cannot be treated. ST cell therapy is now a tremendous game changer for science after many decades of trials. Each experiment showcases a greater ability to use ST cells, but many obstacles remain. Even so, ST cells have a huge impact on regenerative medicine and transplantation. Current therapies can treat neurodegenerative disorders that are currently incurable. When the patient's own cells are induced pluripotent, the cell can become useful. Tissue banks are becoming extremely prevalent as they collect cells which are the source of regenerative medicine in a fight against current and future diseases. Developing therapies and regenerative medicine has contributed to an increase in life expectancy of humans.

1. Introduction

ST cells in multicellular organisms have the ability to self-renew and are potent. This means that they are differentiated or partially differentiated cells with this property. They can also produce a greater number of them of the same kind.

Five to fourteen days after conception, a blastocyst is formed from 50-150 ST cells. They are the basis of all human cells, and at the embryonic stage, these cells are pluripotent. Cells differentiate into three layers during gastrulation, namely endoderm, mesoderm and ectoderm. It is possible to isolate and store these cells, called embryonic ST cells.

STcells collected from an adult are found at some specific locations which are known as niches. Most of these cells are found in the bone marrow and gonads. But these cells are known to have lost the property of pluripotency and they are either unipotent or multipotent. One cell type or several types can be differentiated from one cell type. The ST cells play an important function by replacing the lost cells with the new ones. 3 types of STcells found in adults are

Haematopoietic: - These replenish blood and immune system STcells

Basal cells: - These maintain the skin epithelium

Mesenchymal: - These maintain musculoskeletal cells and fat. This type of cell is very scarce, and it is easily outnumbered.

Nobel prize was awarded to Shinya Yamanaka in the year 2012, for discovering the method of converting mature body cells into STcells by modifying expression of only four genes and these are termed as Induced Pluripotent STcells (iPSCs). This was a major breakthrough in the field of STcells.

2. Unique Properties of Stem Cells

1. Divided or renewed for extended periods of time, they are capable of dividing and renewing themselves.
2. They are not specialised.
3. They can produce function specific cells.

1) They are self-renewable. Using mitosis, they can replicate themselves and reproduce themselves accurately. The daughter cell is exact duplicate of them. They both duplicate within a limited number of generations, but normal cells can duplicate much more often than them.

2) Stem Cells are unspecialised. Therefore, they are not assigned a specific job or function. The skin cells, for instance, help in protecting and forming the first line of defense within our body, the muscle cells contract and help us move, the nerve cells transmit and transduce signals, but the STcells do not have any specific functions. Nonetheless they do have the potential to become various other specialised cells in the body.

3) Differentiation and production of specific cells can be achieved by ST cells. They can differentiate into an organ cell, or also referred to as a somatic cell. They are responsible for forming every type of cell included in our bodies. They can get converted into different other specialised cells through a method known as differentiation. Differentiation thus occurs to transform unspecialised cells into specialised cells such as those useful in blood formation, nerve function, or heart muscle activity.

3. Types of Stem Cells:

3.1. Embryonic Stem

It is known that embryonic ST cells are derived from a blastocyst's inner cellular mass. This means they are derived from the organism's cells. These cells have the capability to change into any various types of cells present in our body. In other words, we can say that they possess a very interesting property known as plasticity. It is said that they are pluripotent.

The two key features are:

1. They have the unique characteristic of pluripotency. The cells can form a wide range of specialized cells because of this ability.
2. They also possess another unique property that allows for continuous self-renewal while retaining its pluripotent properties.

3.1.1. How to get an embryonic stem cell line?

They are grown in the laboratory by a process called cell culture. A laboratory culture dish, commonly called a petri dish, is used to grow them from blastocyst stage embryos. The petri dish is provided with a suitable nutrient broth also called culture medium. These are allowed to divide and duplicate under favourable conditions. Likewise, when they are given favourable conditions they can self-renew in a petri dish. A suitable signalling molecule can also cause differentiation into specialized types of cells. If placed in another petri dish, the group of cells will again divide and produce new cells. Many petri dishes can

become full with the cells that are present in one petri dish. Through this in vitro manner extensive amount of non-differentiated pluripotent cells are made.

3.2. Adult or Somatic Stem Cells

In addition to repairing or regenerating tissues and organs, these cells can also differentiate into specialized cell types. The ability of STcells to self-renew is a property of them. STcells found in adults and children are different from these cells. They help in the repair of the body. As a result, cells and tissues are replenished and regenerated.

Epidermal Stem Cells: Skin cells, for example, are waterproof, rugged and resistant to water. Epithelial cells shed themselves constantly. They fall off during every day activities. Almost 40,000 cells are shed per hour. An individual's skin cell sheds so often that he or she can grow a new layer of skin only once a month. Our skin contains epidermal ST cells, which help us perform this task. The job of these cells is to divide continuously to make new cells, that migrates upward as multiple layers of the skin and replace the damaged outermost layer that gets damaged and fall off. This shows the regenerative role of them.

Hematopoietic Stem Cells: Let us take another example for these cells. It is possible for multipotent cells to self-renew and can produce multiple specialised cell types belonging to a particular family. About four months is the average life span of RBCs in the human body. This means that the blood cells need to be constantly replaced. They are found in the bone marrow of humans. In this case, they are multipotent. New blood cells are made by them. The RBCs are used in carrying oxygen and the WBC are responsible for maintaining the immune system. In the case of cancer, for instance, a patient suffering from leukemia experiences uncontrollable cell growth in their bone marrow. Due to this, not enough blood cells are produced by the unaffected ST cells. In the treatment of leukemia, the affected cells are removed from the body by the help of chemotherapy. This is then followed by a process where more cells are put in the bone marrow of the patient. This results in the formation of more amount of blood in the patient's body again that further go on to produce more amount of blood for the patient again. This treatment proves to be the most commonly practiced use of these cells till date in the field of medicine.

Neural Stem Cells: Neurons and their supporting cells such as astrocytes and oligodendrocytes, if necessary, are produced by the multi potent neural ST cells present in the body.

Mesenchymal Stem cells: Cells of the bone, cartilage, and fat tissues are produced by them. These cells can be found in various places in the body of the humans. Increasing age results in a decrease in cell numbers in the body. As a person grows old, the amount of these cells present in the body are lost or degenerated. In a newborn baby, there are thousands of them, but as the baby grows older, he loses 60% of them by the age of 18. This means that the eighteen year old will have only 40% cells present in the body. This percentage lowers to 25% by the age of 30 years. By the time a person reaches the age of 60 or above, only 5% of these cells are present in the body. Along with the decrease in these cells, age also decreases the functional potential and functionality. Therefore, in comparison with adult ST cells, newborn ST cells have more potent properties and are more likely to divide and differentiate into new cells. It goes without saying that an infant's ST cells are far more potent than those of an adult. (MSCs) are grown-up undeveloped cells which can be separated from human and creature sources. In humans, metastatic ST cells (hMSCs) are non-hematopoietic multipotent undifferentiated cells capable of dividing into osteoblasts, adipocytes and chondrocytes, as well as neural cells (neurons). MSCs express cell surface markers like bunch of separation (CD)29, CD44, CD73, CD90, CD105 and come up short on the statement of CD14, CD34, CD45 and HLA (human leucocyte antigen)- DR. In addition to bone marrow, hMSCs were found in fat tissue, amniotic fluid, endometrium, dental tissues, the umbilical cord, and Wharton's jam, which harbors MSCs.

1) **Osteoarthritis**

Osteoarthritis is a typical, constant, serious degenerative problem of the joints, the space of the skeleton where two bones meet up. Over the long run, ligament, the connective tissue that shapes at the finishes of the bones, wears out, ligaments and tendons weaken, and irritation increments. At the point when this occurs, joints become difficult and hardened. OA can happen in any joint, however is generally normal in knees, hips, spine, and hands. Once ligaments are born, they do not regenerate. Hence, scientists should figure out how ligament is shaped prenatally. Researchers use factors distinguished in early stage joint arrangement to turn pluripotent foundational microorganisms, cells that can turn out to be any cell in the body, into ligament. Subsequent to seeing how joints are shaped during early stage improvement, researchers can attempt to utilizing cells in the lab to fix harmed ligament or by actuating cells in the patient to frame new ligament. Researchers are effectively attempting to recognize approaches that can securely and successfully fix harmed joints. iPS cells can

be derived from OA patients, which have their exact genetic makeup, which can be used to form cartilage that can be used to study OA, allowing researchers to better understand the genetic basis of the disease.

In embryonic ST cells, there are some key differences compared to adult ST cells

	Embryonic Stem Cells	**Adult Stem Cells**
1. Potency	In other words, embryonic ST cells are pluripotent, which means they can divide and differentiate into every type of cell in the human body.	Multiple specialized cells can be produced from adult ST cells, but they must be of equal origin.
2. Isolation and Cell culture.	Embryonic STcells can easily be grown in a culture.	It is difficult to isolate adult ST cells from tissues and the culturing of these stem cells has not yet effectively been worked upon.
3. Immune rejection	It is more likely that tissues or organs grown from embryonic ST cells will be rejected by the immune system.	As adult ST cells originate from their own ST cells, the chances of immune rejection for derived tissues or organs decrease.
4. Controversial	Despite the controversy, the safety of these cells could be improved by separating the ST cells from the inner cell mass.	No such damage can be caused to the embryo as the cells are isolated from the adult. Thus, it is not unethical or controversial.

3.3 Induced Pluripotent Stem Cells (iPSCs)

Pluripotent STcells are differentiated mature cells which possess specific genes that enable them to lose the features they were born with and become pluripotent. The muscle cells, neural cells, bone cells, etc., can be generated by them, since they are pluripotent.

Repairing damage to the body through regenerative medicine can be undertaken with STcells taken from the patient's own body. A patient who receives his or her cell line of induced pluripotent STcells will be able to restore and repair damaged tissue. By using their own cells to make new organs, this not only provides a patient with a new organ but also reduces the chances of the body rejecting it. This is possible because the new organs are made from their own cells.

The Nobel Prize was awarded to Dr. Shinya Yamanka in 2012 in recognition of the exploration of stimulated pluripotent ST cells (iPSCs). Following successful transfer of mouse skin cells into embryonic ST cells in 2006, scientists were able to generate embryonic STcells from mouse skin cells. This cell was designated as induced pluripotent ST cell (iPSCs). This was done by a very basic process. When transduced by a retrovirus, four transcription factors were able to convert the skin cells of mice back into ST cells, including Oct3/4, Sox2, Klf4 and c-myc.

Researchers have also generated iPSCs from human skin cells in 2007.In the starting only the skin cells were used to make iPS cells but now, many types of somatic cells can be used to make iPSCs . iPSCs are most often made from blood cells today. Using the four transcriptional factors above, it is possible to convert lymphocytes in the blood into iPS cells. From these iPSCs, a number of different types of cells can be formed.

3.3.1 Advantages and Disadvantages Of iPS cells

Advantages:

- In contrast to embryonic STcells, they do not damage the embryo because they are not derived from embryos or they do not cause harm to the embryo.
- iPSCs can directly be acquired by blood sampling. In a blood vial, iPSCs can be produced that can form different types of cells.
- Transplantation of these cells is possible as well. It is collected from patients which have developed into differentiated cells. Transforming it into pluripotent tissue is possible when the four transcription factors are introduced. Upon transplantation of these, a specific type of organ is formed and then transferred into the patient. It is less likely that an immune system will reject the transplanted cell or organ this way.

Disadvantages:

These are the disadvantages:

- When it comes to working with iPS cells, its safety is the most crucial issue. A patient's iPS cells can be created by separating them from the patient's somatic cells and then they can be transformed into transplantable cells. The patient may later be affected by mutations resulting from this process. Recently, there has been research for extracting the virus after transferring the genes, rather than permanently introducing it into the cell. Therefore, mutations are less likely to occur.
- However, there has not been any clinical practice with iPSCs. Only one clinical trial took place that was later on suspended.
- Although it is not yet effective in medicine, it may be helpful in regenerative medicine in the future.

3.3.2 Applications of iPS cells

- A vast collection of ST cells known as biobanks are made using the induced ST cells at present. These cells can be utilized for any kind of transplantation. This is being done throughout the world.

- As well as studying about the unique diseases caused by genetics, they are used to study them. One such disease is Progeria, a rare disorder in children that affects one in every twenty million which is characterised by premature aging. The patient's body provides the cells. Cells that are taken from patients are reprogrammed and in vitro grown since they contain the genetic makeup of the disease. This is done in order to study the underlying mechanism of the disease.

- Based on them, regenerative medicine can be practiced. This is designated as ST cell therapy. This refers to picking of cells from the patient, inducing it to pluripotent state and then transforming it to the cells of the organ that has to be transplanted into the patient. This is then moved into the patient’s body by the help of transplantation.

- Moreover, they are crucial to the development of drugs. It is possible to create several kinds of cells by transforming ST cells in this way. For instance, a number of liver cells, or muscle cells or heart cells, can be produced in the laboratory by the use of iPS cells. This is really useful in the field of drug development for many diseases.

  IPSCs can be used to treat many incurable diseases, but their full potential is not yet known. With the advancement of scientific technologies, these iPSCs hold a very important role in the field of regenerative medicine and ST cell therapy.

4. Possible uses Of Stem Cells and the problems to be overcome before it is actually used

It is possible to utilize ST cells in clinics and laboratories in various ways. The study of ST cells present in our bodies will allow us to explore the numerous abilities these cells have within the body and explore how they

may be used to help treat disease and conduct research. In recent years, many studies and discoveries have been made on the use of these cells for recovery and treating many diseases. Despite being fully realized, ST cells have yet to be used in clinical trials in spite of their many beneficial characteristics. The increasing technologies and ongoing research may provide ST cell treatments for many incurable diseases. Cell-based therapies could also be used in the near future.
Early in the embryonic development, human embryonic STcells exist. Human development can be further understood by studying ST cells. The study will help to clarify how nontransformed cells differentiate into transformed cells that form tissues and organs. The unusual division and transformation of cells can result in congenital defects, tumors and cancer. Researchers discovered that IPSCs contain a number of distinct transcription factors; however, with the development of new technologies and research, many new techniques are needed to introduce these transcription factors and genes into these cells. These factors will thereby be controlled and can help control the process.

The STcells can also be helpul in the field of drugs and pharmaceutics. In order to use a drug to treat disease, it must be validated as effective and also analyzed to see if there are possible side effects of its usage. Because of this, ST cells are playing an increasingly important role in the drug-testing process. STcell lines are being used by scientists to study the potential of new drugs. The lines of cancer cells can be used to test drugs that fight cancer. iPSCs have been found to be in favor of this hypothesis. There are a variety of cell types and lines that can be produced from iPSCs. Therefore, new drugs can be tested on a wider range of cell types. Although there is one challenge that the scientists need to overcome. The conditions should be identical for the comparison of different drugs. Thus, the scientist needs to cautiously differentiate the cells into the required cell type on which the drug has to be tested.

Among the most important applications of STcells are cell therapies. Currently, damaged organs and tissues are transplanted using donated organs. Nonetheless, there are much fewer donated organs than those that are transplanted. Because they possess the capability to differentiate into various cell types, they can function to replace damaged tissues and damaged cells. Burns, spinal cord injuries, stroke, diabetes, macular degeneration, arthritis, etc. can all be greatly improved with this kind of therapy. This will reduce the reliance on donated organs for transplants, as the transplanted cells will be formed from the recipient's own body, thus resulting in almost negligible immune rejection. Researchers have developed a method for making iPS cells from blood that could be used to cure blood related diseases such as leukemia, thalasemia, etc. The technique could be used in the future to generate a whole organ in-vitro, like a heart, and transplant it into a patient's body.
To sum up, they hold a great potential and can be used for enormous future treatments and therapies, but before that, extensive research is required in order to use this technology for clinical purposes.

5. The future of Stem Cell Biology

As well as treating a wide range of congenital defects and other harmful diseases, ST cells offer tremendous potential and opportunity. Regenerative medicine and ST cell therapy utilize STcells as the central component of their emerging fields. The STcells have been known to have the potential to develop into any kind of cells present in the body. In this manner, they may eventually be used to regenerate damaged organs and tissues, allowing humans to live a longer, healthier life. Any damaged organ or tissue can be repaired or replaced with ST cell therapy in the future. This branch of biology holds great promise for both transplantation and replacement therapies. Patients suffering from a range of injuries and diseases may benefit from them. A breakthrough in this came when researchers discovered iPSCs. In the future, iPSCs will be used to develop many types of specialised cells, which will serve as an essential tool for regenerative medicine. They also hold great scope in the field of drug development. It will be possible in the future for medical and pharmaceutical agents to activate ST cells, promote the migration of ST cells to the site of injury, and to stimulate the differentiation of STcells into specialised cells. Using STcells in the therapy of diseases such as cancer, tumors, muscle damage, autoimmune diseases, myocardial infarction and heart-related problems, spinal cord injuries, and other ailments will likely be of great advantage in the future with the development of technologies. Despite the fact that they have not been fully exploited, studies show that ST cells can benefit regenerative medicine and cell-based therapies for treating and curing conditions.

Conclusion

Regenerative medicine, in its evolving field, is likely to benefit greatly from STcells. The potential uses must be discovered first by overcoming the various barriers that surround them. The potential of these cells in regenerative medicine remains largely untapped. Much still needs to be accomplished before their full

capabilities can be realized. As a result of preclinical studies on animal models, patients are hopeful about STcell therapies coming to pharmacies soon. Research and experiments over so many years have proven that they are a revolutionary advance in medicine. The research has shown a lot of promise, but all of the barriers to its use must be overcome first. With advancements in research, patients may be able to treat many diseases that are currently untreatable. A procedure known as induced pluripotent ST cell therapy uses a patient's own ST cells. STcell banks are being used to fight a range of future diseases. As a result, STcells are essential for conceiving and improving medical therapies.

References

1. Mulligan R.C. The basic science of gene therapy. Science. 1993; 260:926–932. - PubMed

2. Bajada S, Mazakova I, Richardson JB, Ashammakhi N. Updates on stem cells and their application in regenerative medicine. J Tissue Eng Regen Med. 2008;2(4):169–83. [PubMed] [Google Scholar]

3. Molofsky AV, Pardal R, Morrison SJ. Diverse mechanisms regulate stem cell self-renewal. Curr Opin Cell Biol. 2004;16(6):700–7. [PubMed] [Google Scholar]

4. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–76. [PubMed] [Google Scholar]

5. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–72. [PubMed] [Google Scholar]

6. Yu J, Vodyanik M, Smuga-Otto K, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318(5858):1917–20. [PubMed] [Google Scholar]

7. Park IH, Zhao R, West JA, et al. Reprogramming of human somatic cells to pluripotency with defined factors. Nature. 2008;451(7175):141–6. [PubMed] [Google Scholar]

8. Aoi T, Yae K, Nakagawa M, et al. Generation of pluripotent stem cells from adult mouse liver and stomach cells. Science. 2008 Epub ahead of print. [PubMed] [Google Scholar]

9. Nakagawa M, Koyanagi M, Tanabe K, et al. Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. Nature Biotech. 2008;26(1):101–106. [PubMed] [Google Scholar]

10. Good RA, Meuwissen HJ, Hong R, Gatti RA. Bone marrow transplantation: correction of immune deficit in lymphopenic immunologic deficiency and correction of an immunologically induced pancytopenia. Trans Assoc AM Physicians. 1969;82:278–85. [PubMed] [Google Scholar]

11. Kogler F, Sensken S, Airey JA, et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med. 2004;200(2):123–35. [PMC free article] [PubMed] [Google Scholar]

12. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell. 2003;114(6):763–76. [PubMed] [Google Scholar]

13. Greenfield JP, Ayuso-Sacido A, Schwartz TH, et al. Use of human neural tissue for the generation of progenitors. Neurosurgery. 2008;62(1):21–37. [PubMed] [Google Scholar]

14. Wobus AM. Potential of embryonic stem cells. Mol Aspects Med. 2001;22:149–64. [PubMed] [Google Scholar]

15. Yamanaka S, Jinliang Li, Kania G, et al. Pluripotency of embryonic stem cells. Cell Tissue Res. 2008;331:5–22. [PubMed] [Google Scholar]

16. National Institutes of Health resource for stem cell research. [May 28, 2008];The stem cell information appendix C page. Available at: http://stemcells.nih.gov/info/scireport/appendixC.asp.

17. Yang L, Soonpaa MH, Adler ED, et al. Human cardiovascular progenitor cells develop from a KDR+ embryonic-stem-cell-derived population. Nature. 2008;453(7194):524–8. [PubMed] [Google Scholar]

18. Laflamme MA, Chen KY, Naumova AV, et al. Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infracted rat hearts. Nat Biotechnol. 2007;25(9):1015–24. [PubMed] [Google Scholar]

19. Zhuo BH, Li TY, Jiang HB, Qu P, Liu Y. The effect of all-trans retinoic acid on the differentiation of marrow stromal stem cells into neurons. Acta Nutrimenta Sinica. 2005;27(3):189–92. [Google Scholar]

20. Pittenger M.F., Mackay A.M., Beck S.C., Jaiswal R.K., Douglas R., Mosca J.D., Moorman M.A., Simonetti D.W., Craig S., Marshak D. R. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284:143–147. Doi: 10.1126/science.284.5411.143. [PubMed] [CrossRef] [Google Scholar]

21. Crisan M., Yap S., Casteilla L., Chen C.W., Corselli M., Park T.S., Andriolo G., Sun B., Zheng B., Zhang L., et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell. 2008;3:301–313. Doi: 10.1016/j.stem.2008.07.003. [PubMed] [CrossRef] [Google Scholar]

22. Dominici M., Le Blanc K., Mueller I., Slaper-Cortenbach I., Marini F., Krause D., Deans R., Keating A., Prockop D., Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8:315–317. Doi: 10.1080/14653240600855905. [PubMed] [CrossRef] [Google Scholar]

23. Wagner W., Wein F., Seckinger A., Frankhauser M., Wirkner U., Krause U., Blake J., Schwager C., Eckstein V., Ansorge W., Ho A.D. Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. Exp. Hematol. 2005;33:1402–1416. Doi: 10.1016/j.exphem.2005.07.003. [PubMed] [CrossRef] [Google Scholar]

24. Zhang X., Yang M., Lin L., Chen P., Ma K.T., Zhou C.Y., Ao Y.F. Runx2 overexpression enhances osteoblastic differentiation and mineralization in adipose–derived stem cells in vitro and in vivo. Calcif. Tissue Int. 2006;79:169–178. Doi: 10.1007/s00223-006-0083-6. [PubMed] [CrossRef] [Google Scholar]

25.Mokbel AN, El Tookhy OS, Shamaa AA, et al. Homing and reparative effect of intra-articular injection of autologus mesenchymal stem cells in osteoarthritic animal model. BMC Musculoskelet Disord. 2011;12:259. [PMC free article] [PubMed] [Google Scholar] This study used chemically induced OA in donkeys to investigate the appropriate timing of direct stem cell injection to the knee, which will be critical for establishing which patients may benefit from such strategies.

26. Ansboro S, Greiser U, Barry F, Murphy M. Strategies for improved targeting of therapeutic cells: implications for tissue repair. Eur Cell Mater. 2012;23:310–319. [PubMed] [Google Scholar]

27. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem. 2006;98:1076–1084. [PubMed] [Google Scholar]

28. Prockop DJ, Oh JY. Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation. Mol Ther. 2012;20:14–20. [PMC free article] [PubMed] [Google Scholar]

29. Lee DH, Sonn CH, Han SB, et al. Synovial fluid CD34(−) CD44(+) CD90(+) mesenchymal stem cell levels are associated with the severity of primary knee osteoarthritis. Osteoarthritis Cartilage. 2012;20:106–109. [PubMed] [Google Scholar]

30. Sekiya I, Ojima M, Suzuki S, et al. Human mesenchymal stem cells in synovial fluid increase in the knee with degenerated cartilage and osteoarthritis. J Orthop Res. 2012;30:943–949. [PubMed] [Google Scholar]

31 Johnson K, Zhu S, Tremblay MS, et al. A stem cell-based approach to cartilage repair. Science. 2012;336:717–721. [PubMed] [Google Scholar]

32. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663–76. [PubMed] [Google Scholar]

33. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131:861–72. [PubMed] [Google Scholar]

34. Yu J, Vodyanik MA, Smuga-Otto K, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318:1917–20. [PubMed] [Google Scholar]

35.Nakagawa M, Koyanagi M, Tanabe K, et al. Generation of induced pluripotent stem cells without myc from mouse and human fibroblasts. Nat Biotechnol. 2008;26:101–6. [PubMed] [Google Scholar]

36. Shi Y, Desponts C, Do JT, Hahm HS, Scholer HR, Ding S. Induction of pluripotent stem cells from mouse embryonic fibroblasts by oct4 and klf4 with small-molecule compounds. Cell Stem Cell. 2008;3:568–74. [PubMed] [Google Scholar]

37. Huangfu D, Maehr R, Guo W, et al. Induction of pluripotent stem cells by defined factors is greatly improved by small-molecule compounds. Nat Biotechnol. 2008;26:795–7. [PMC free article] [PubMed] [Google Scholar]

38. Huangfu D, Osafune K, Maehr R, et al. Induction of pluripotent stem cells from primary human fibroblasts with only oct4 and sox2. Nat Biotechnol. 2008;26:1269–75. [PubMed] [Google Scholar]

39. Wernig M, Meissner A, Foreman R, et al. In vitro reprogramming of fibroblasts into a pluripotent es-cell-like state. Nature. 2007;448:318–24. [PubMed] [Google Scholar]

40. Meissner A, Wernig M, Jaenisch R. Direct reprogramming of genetically unmodified fibroblasts into pluripotent stem cells. Nat Biotechnol. 2007;25:1177–81. [PubMed] [Google Scholar]

41. Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. Nature. 2007;448:313–7. [PubMed] [Google Scholar]

42. Kobold S., Guhr A., Mah N., Bultjer N., Seltmann S., Seiler Wulczyn A.E.M., Stacey G., Jie H., Liu W., Loser P., et al. A Manually Curated Database on Clinical Studies Involving Cell Products Derived from Human Pluripotent Stem Cells. Stem Cell Rep. 2020;15:546–555. Doi: 10.1016/j.stemcr.2020.06.014. – DOI – PMC – PubMed

43.Schwartz S.D., Hubschman J.P., Heilwell G., Franco-Cardenas V., Pan C.K., Ostrick R.M., Mickunas E., Gay R., Klimanskaya I., Lanza R. Embryonic stem cell trials for macular degeneration: A preliminary report. Lancet. 2012;379:713–720. Doi: 10.1016/S0140-6736(12)60028-2. – DOI – PubMed

44. Ben M'Barek K., Monville C. Cell Therapy for Retinal Dystrophies: From Cell Suspension Formulation to Complex Retinal Tissue Bioengineering. Stem Cells Int. 2019;2019:4568979. Doi: 10.1155/2019/4568979. – DOI – PMC – PubMed

45. Ghareeb A.E., Lako M., Steel D.H. Coculture techniques for modeling retinal development and disease, and enabling regenerative medicine. Stem Cells Transl. Med. 2020;9:1531–1548. Doi: 10.1002/sctm.20-0201. – DOI – PMC – PubMed