# Summary & Conclusions

Stem cell is a cell that has three specific characters: 1) Self renewal 2) Remaining in the undifferentiated state 3) Differentiation potential to be a specialized cell. So it has the ability to divide for indefinite periods. Under the right conditions, stem cells can give rise to the many different cell types that make up the organism. That is, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions, such as heart cells, skin cells, or nerve cells.

In humans, they have been identified in the inner cell mass of the early embryo, in some tissues of the fetus, the umbilical cord and the placenta and in several adult organs. Each comes from different sources and has some what different properties. The embryonic stem cells are usually taken from the blastocyst stage. Fetal stem cells usually accumulate in the liver so fetal liver tissue has been shown to be a rich source of stem cells.

Adult Stem cell is a stem cell that has developed beyond the embryonic state and usually resides in tissue. It is still in an undeveloped state but has a potential to differentiate into the specific cell type.

## A-Embryonic stem cell:

Embryonic stem cell or ES cell is a cell from the inner cell mass of the developing blastocyst. It has an ability to differentiate into all kinds of cell types. In addition, it is also immortal by self renewal capability. Consequently, ES cell is more promising as a therapeutic tool because it has less limitation on differentiation potential.

ES cells have the ability to remain undifferentiated and proliferate indefinitely in vitro while maintaining the potential to differentiate into derivatives of all three embryonic germ layers. They are derived from the inner cell mass (ICM) of blastocysts at a stage (4 to 5 day of a human embryo) before it would implant in the uterine wall. ES cells have been isolated from primate human, but also non-human (rhesus monkey) – blastocysts, cultured and maintained in vitro; thereby providing an unlimited source of ES cells for cellular therapy.

The derivation and maintenance of ES cells in vitro require special culture conditions to remain undifferentiated. Human ES (hES) cells are grown on mouse embryonic fibroblast feeder layers, and in the presence of various reagents of animal origin, e.g., coating substrates, serum. Such culture conditions are not without limitations. Recently, it was reported that mouse feeder layers and/or media used for culturing hES cells could lead them to incorporate N-glycolyl-neuraminic acid residues present in these animal sources. N-glycolyl-neuraminic acid is a sugar present on the surface of most mammal and rodent cells, but is lacking in humans, and against which most humans have circulating antibodies.

The incorporation of N-glycolyl-neuraminic acid residues on hES cell lines would result in the rejection of the graft, thereby, limiting the use of existing hES cell lines for cellular therapy, and mandating for the generation of new cell lines devoid of animal contaminants. So, protocols have been devised for culturing hES cells on autogeneic feeder layer, free of feeder layer. Recently, new hES cell lines have been derived free of feeder layer and animal serum. New hES cell lines free of animal contaminants may offer a source of tissue for cellular therapy.

**Technical challenges ahead**

There are several challenges to ES cell research & therapy. Some investigators have reported that hES cells do not maintain their normal karyotypes, while others have confirmed that some established cell lines remain stable overtime. Though the incidence of such instability on the behavior of the cells and their ability to differentiate is not well understood, established cell lines must be maintained under standard culture conditions, and be checked overtime for normal chromosomal content.

ES cells have also the potential to form tumor upon grafting. The formation of teratoma would be associated with the undifferentiated state of the ES cells. To overcome the risk of tumor formation, it is proposed to pre-differentiate the ES cells *in vitro* to the desired lineage, and to remove the cells that have not differentiated from the cellular graft prior to grafting. Protocol leading to a 100% differentiation, or purification by positive selection by isolating the differentiated cells from the culture would provide alternative strategies to this aim.

Cell surface markers and fluorescent activated cell sorting are strategies that are considered for eliminating undifferentiated cells, and have been successfully tested in experimental setup, as well as protocols leading to high yield of differentiated ES cells, such as differentiated oligodendrocytes.

A third challenge is the potential immunogenicity of the hES cell lines. hES cell lines are allogenic cell lines, derived from blastocysts. To limit the risk of rejection by the patient, upon transplantation, would require matching the donor and recipient genetic make-up. Patients may

also follow immunosuppressive treatments, such as treatment with cyclosporine. An alternative would be to generate isogenic hES cell lines from the patients by somatic cell nuclear transfer (SCNT).

SCNT consists in isolating nucleus of a somatic cell type (fibroblast for example) harvested from the future recipient into an enucleated oocyte. By mechanisms still unknown, the cytoplasm of the oocyte reprograms the chromosomes of the somatic cell's nucleus. The cloned cell develops into a blastocyst from which ES cells can be derived, that carries a set of chromosomes identical to that of the donor, and therefore is unlikely to be rejected by that donor/future recipient.

In February 2004, Dr Hwang Woo-suk and his colleagues in South Korea reported that they had successfully cloned 30 human embryos, from which they had extracted stem cell lines. In May 2005, Hwang and his team published a paper claiming they had made 11 patient-specific cell lines using donated eggs and the DNA from people suffering from diseases such as juvenile diabetes and spinal cord injury. However, both of these papers have now been shown to contain fraudulent data and have been retracted by the publisher, Science magazine. Ethical issues have been raised by this scandal.

**Ethical and political challenges ahead**

1) Concerning the issue of destroying the embryos and its legibility.
2) Regulations for using stem lines and its control.

**Advantages over other types of stem cell "why it's important?"**:

As mentioned before, it's derived from a more primitive stage than the fetal and adult stem cell; so, it has more power to differentiate into

any type of tissue. It's easier to culture and finally it can be used in gene therapy.

## B-Fetal stem cell:

Due to the ethical dispute and safety issues surrounding the potential clinical use of embryonic stem cell, other sources of stem cells have been encouraged. Fetal stem cells are nothing new. Umbilical cord blood haemopoietic stem cells have been extensively investigated and widely utilized over the last 10 to 20 years and fetal neural tissue has already been used therapeutically in parkinson's disease, with some evidence of clinical improvement.

Fetal stem cells can be isolated from fetal blood and bone marrow as well as from fetal blood are similar to their adult counterparts but might have greater expansion and differentiation potential due to higher telomerase activity which protects against ageing and give additional advantages in cell replacement therapies.

Fetal blood is both a source of haemopoietic stem cells, which proliferate more rapidly than those in cord blood or adult bone marrow, and a source of non-haemopoietic mesenchymal stem cells, which support haemopoiesis and can also differentiate along multiple lineages.

**Potential applications of fetal stem cells:**

1- Non invasive prenatal diagnosis: using fetal stem cells derived from maternal blood to determine fetal gender and detect inherited genetic disease.

2- Treatment of the fetus in utero using stem cells: using them either in:
(a) In utero transplantation: overcoming the limitations of postnatal therapy as it have the advantages of fetal immunological immaturity, a sterile fetal environment and early inhibitions of disease progression.
(b) Gene therapy: ex vivo gene therapy uses autologous HSC that are obtained from the fetus, transduced in vitro and then transplanted back to the fetus.
(c) Fetal Microchimerism: this is defined as the presence of low levels of fetal cells harboring in maternal blood and tissues for years after pregnancy.

## C-Adult stem cells:

An adult stem cell is an undifferentiated cell that is found in a differentiated (specialized) tissue in the adult, such as blood. It can yield the specialized cell types of the tissue from which it originated. Recently, adult stem cells from one tissue appear to be capable of developing into cell types that are characteristic of other tissues.

For example, although adult haemopoietic stem cells from bone marrow have long been recognized as capable of developing into blood and immune cells, recently scientists reported that under certain conditions, the same stem cells could also develop into cells that have many of the characteristics of neurons. At this point there's no population of adult stem cells that is capable of forming all the kinds of cells of the body.

The main differences between embryonic and adult stem cells are that embryonic stem cells can produce relatively large numbers of stem

cells and easily grown in relation to adult stem cells which needs large numbers of cells for cell replacement therapies. A potential advantage of using stem cells from an adult is that the patient's own cells could be expanded in culture and then reintroduced into the patient. The use of the patient's own adult stem cells would mean that the cells would not be rejected by the immune system.

Nowadays, the widely recognized clinical applications of adult stem cell are bone marrow hemopoietic stem cells, which were used for bone marrow transplantation in leukemia, anemia, autoimmune diseases and immunodeficiency cases. Also ovarian stem cells and their use as a potential treatment for ovarian infertility, prevention of premature ovarian failure after chemotherapy and treatment of degenerative diseases.

## D-Haemopoietic stem cell:

Is a cell isolated from the blood or bone marrow that can renew itself, can differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death. Sources of haemopoietic stem cells include: Bone marrow, peripheral blood and umbilical cord blood. Umbilical cord blood advantages over other HSCs sources can be summarized in that they can be the only source of allogenic HSCs available to patients with rare HLA types and for urgent unrelated donor transplants, with less GVHD and also a lower risk of transmission of latent viruses.

# CONCLUSIONS

Stem cells have been categorized according to their origin into: Embryonic, fetal, adult and hemopoietic stem cells (including cells of other types). The cells are different but share some common features which put them all in a single pot known as stem cells and present immense research opportunities for potential therapy.

During the next several years, it will be important to compare embryonic, fetal and adult stem cells in terms of their ability to proliferate, differentiate, survive and function after transplantation and avoid immune rejection. Scientists upon making new discoveries often verify reported results in different laboratories and under different conditions.

Similarly, they will often conduct experiments with different animal models or in this case, different cell lines. However, there have been very few studies that compare various stem cell lines with each other. It may be that one source proves better for certain applications, and a different cell source proves better for others.

Although embryonic stem cells proved to give rise to cells derived from all the three germ layers, but still this high differentiation capacity has the disadvantage of forming teratomas. Although it is the most tested & practiced, most of the applications & cultures are still in animal models also it raises the concern about the ethical dispute surrounding it and the same is with fetal stem cells.

Adult stem cells have the advantage of being from adult tissue which may be derived even from the same person which needs cell replacement therapy with less GVHD & also the ethical dispute surrounding it is much less but didn't provide the differentiation capacity as the embryonic or the fetal, and it provides less numbers of cells and it's the hardest type to be cultured. It's the least tested type & needs further research.

As for hematopoietic stem cells: It's the most applicable as for bone marrow stem cells, peripheral blood stem cells and also for the cord blood stem cells which begin to flourish now with the development of umbilical cord blood banks but it's application and its cost-effectiveness is still questionable !!

Predicting the future of stem cell applications is impossible, particularly given the very early stage of the science of stem cell biology. How many different sources of stem cells will be needed to generate the best treatments in the shortest period of time??

The answer is still vague, and further research is needed for the picture to become clearer.