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RESEARCH ARTICLE

IS IT POSSIBLE TO REGENERATE THE BRAINS OF CLINICALLY DEAD PEOPLE

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ABSTRACT

When the heart stops the blood supply to the brain is quickly cut off – and in operating theatres this moment would be recorded as the official time of death. But studies show that the dead person's mind and consciousness continue to work, at least for a short time – meaning the deceased can recognize their own death. Stem cells can remain alive in human corpses for at least 17 days after death, researchers say. Indeed there is some evidence to suggest the 'dead person' may even hear their own death being announced as they lie on the operating theatre table. Stem cells are self-renewing, undifferentiated, non-committed, primitive cells till they receive a signal to develop into specialized cells, a stem cell cannot work with its neighbour to pump blood nor it can carry oxygen but it can differentiate into those cells that does this function. Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth in addition in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cell as long as the person or animal is still alive. When a stem cell divides each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle, a red blood cell or a brain cell. Research on stem cells continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of the most of the fascinating areas of contemporary biology, but as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

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INTRODUCTION

Undifferentiated cells having potential to both self renew and differentiate to produce mature progeny cells. Recent perspective, the concept of "stem cells" is indissolubly linked with growth via the multiplication rather than the enlargement of the cells. Various schemes for classifying tissues according to their mode of growth have been proposed. This classification, which relates to the situation in the adult rather than in the embryo, recognizes three basic types of tissues: renewing, expanding, and static. Obvious examples of the first are intestinal epithelium and skin, and of the second, liver. The third category was held to include the central nervous system, although recent studies shown that neurogenesis does continuing adulthood, for example with, with regard to production of neurons that migrate to the olfactory bulbs. There are various problems with such schemes of classification including, for instance assignment of organs like the mammary gland which, depending in the circumstances of the individual, may engage in one or more cycles of marked growth, differentiation, and subsequent involution. Diseases like childhood leukaemia, Alzheimer's, neural degenerative disease like Parkinson's, as well Thalassemia, Diabetes, Spinal cord injury, are not curable with existing therapies. The potential to cure otherwise "incurable" diseases like Parkinson's or leukaemia is now greater than before and at least most of them if not at all, without relying on conventional therapies. Science had been progressing continuously because there is always a tremendous necessity in treatment of such diseases. Any attempt to find a universally acceptable definition of the term stem cell is probably doomed to fail. Nonetheless, certain attributes can be assigned to particular cells in both developing and adult multicellular organisms that serve to distinguish them from the remaining cells of the tissues to which they belong. Most obviously, these cells retain. Stem cells multipotent cells have the remarkable potential to develop into many different cell types in the body during early life growth. Also, in many tissues they serve as a store of internal repair

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system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive (Carlen, 2002). When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell (Carleton, 2003). Stem cells differ from other kinds of cells in the body. All stem cells-regardless of their source-have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized, and they can give rise to specialized cell types (Doetsch, 1997). There are several sources of stem cell used in the clinical application including as therapeutics. The bone marrow is a key source of stem cell and gives raise various kinds of other cells for different physiological functions (Doetsch, 1997). Additionally, embryonic stem cells believed as a prime source of stem cell, and during embryonic development, all types of human tissues and cells are derived from there layers of the embryo as the source of stem cell is highly regulated and faces various ethical issues as well (Doetsch, 1999).

The molecular biology plays an important role in the harvesting these multipotent cells for various therapeutic applications. The stem cells despite from their varying source are embryonic stem cells are believed most efficient and robust stem cells. The umbilical cord blood, bone marrow, and adipose tissues are a potential source of stem cells (Eriksson, 1998). The stem cell preservation especially cords blood is a quite common technique to store stem cell for future applications. These cells are present in a very limited amount, and their regeneration is dependent on several factors; stimulatory signals and nutrients. Stem cells have a long history and initially derived from other animals like mice and rodents (Eriksson, 1998b). However, their clinical applications in context to human are highly limited, and hence human stem cells were investigated for their potential sources and harvesting methods. The uses of stem cell in modern medicine are increasing and have shown a promising result as well. There are several stem cell therapies under clinical trials studies (Evans, 1981). In case of several diseases where conventional medicine faces difficulty to find cure stem cell technology have a great scope not only in diseases management but also tissue regeneration (Fusaki, 2009). The vital tissues including brain, liver, heart, kidney, and lungs entirely depend on stem cell biology. Additionally, the use of stem cell in the production of blood and its components; cellular component in transfusion medicine have a great scope. The chimeric research (human-animal chimeras and animal chimeras) is possible due to recent advancement in stem cell biology and associated cutting edge of molecular biology. Cell potency is a cell's ability to differentiate into other cell types. Not at all the human cells have the potency, and a few have selected potency as well.

The cell potency is a unique feature of a cell to divide and differentiate into other types of cells. The classical example is zygote undergoes a rapid differentiation and develops a pool of cell to grow a complete organism (Gould, 1999). Stem cells can be classified by the extent to which they can differentiate into different cell types like Totipotent, Pluripotent, Multipotent, and Unipotent. Totipotency is the ability of a single cell to divide and produce all the differentiated cells in an organism. Spores and zygotes are examples of totipotent cells. In the spectrum of cell potency, totipotency is the genetic potential of a cell to produce the entire organism. In other words, totipotency is the cell characteristic in which the potential for forming all the cell types in the adult organism retained (Gurdon, 1962). The embryonic stem cells can become a cell for any pary of the body is called pluripotent. The difference between totipotent and pluripotent cells is only that totipotent stem cell can give ride to other types of cells, and the embryo. A multipotent stem cell can give rise to other types of cells but it is limited in its ability to differentiate (Kempermann, 2011). These other types of cells, are also limited in numbers. Examples of multipotent stem cells include those in the brain that give rise to different neural cells and glia or hematopoietic cells, which can give rise to different blood cell types, but they can't create brain cells (Kornack, 1999). Bone marrow also contains multipotent stem cells that give rise to all blood cell types but no other cells. These are numerous benefits and uses multipotent stem cells. Since multipotent stem cells derived from pluripotent stem cells, these stem cells have already partially differentiated, and they continue specializing as they develop (Kuhn, 1996).

A unique property of stem cells is their ability to differentiate, which means they can form specialized cells. Another special property is their ability to proliferate or divide repeatedly. As mentioned, unipotent cells have a very limited ability to differentiate relative to other stem cells such as pluripotent, totipotent or multipotent cells (Lois, 1996). Their ability to self-renew, however, does make them a valuable candidate for therapeutic use in treating disease. They are thus able to generate healthy and viable cells for transplant purposes. Unipotent stem cells arise from multipotent cells. A multipotent stem cell is one can develop into a limited number of tissue rise to almost any specialized cell in the body (Eriksson, 1998a). A unipotent stem cell will start to differentiate and give rise to a specific stem cell. The tissue-specific cell will then provide functional and structural components to a body tissue or organ. Skin cells, which are in the epithelium, are one of the most abundant types of unipotent stem cells. The epithelium is the outermost tissue layer, which in itself has a top layer of dead squamous epithelial cells. This is similar to the mucous membranes that line our mouths and other body cavities. By taking a portion of a patient's own undamaged skin stem cells, sheets of skin can be developed for transplanting for burn victims, particularly considering the pain and disfigurement that many burn victims are forced to experience during and fatter healing (Ming, 2005). A major can take several weeks to grow a sufficiently sized piece of skin. Skin is an initial barrier to disease, so the pressure to promote healing and replace burned conditions to encourage unipotent stem cell growth should hopefully ensure that the success of these forms of therapy grows. The process of collecting (harvesting) stem cells for transplant depends on the source of the stem cells. Stem cells can be collected from bone marrow, circulating (peripheral) blood or umbilical cord blood. The stem cell harvesting is collection cells and purification of stem cells.

The purified stem cells were grown in HEK media and other nutrients media based in nature of stem cell. There are no separate methods for stem cell harvesting, and the only difference is screening and growth of selected stem cells (Rakic, 1972). The bone marrow and blood cells, adipose tissues are ideal somatic sources of stem cells. I case harvesting stem cells from blood need a density gradient centrifugation where all the blood cells from blood need a density gradient centrifugation where all the blood cells,

adipose tissues are ideal somatic sources of stem cells. In case harvesting stem cells from blood need a density gradient centrifugation where all the blood cells differentiate based on their size and shape in density column. Similarly, stem cells from bone marrow and other somatic tissues ate harvested based in cellular morphology. Stem cells can be reliably identified and accurately measured because they have a specific marker or label on the stem cell surface (Reynolds, 1992). This marker referred to as the CD34 antigen -positive stem cells is Important because doctors can accurately predict how fast the bone marrow recovers after high-dose chemotherapy administration based on the number of CD34-posirive stem cells infused. Daily measurement of the CD34+ peripheral blood stem cell content is also useful in determining the number of days to perform apheresis. After many months of growth in culture dishes, these remarkable cells maintain the ability to form cells ranging from muscle to nerve to blood-potentially any cell type that makes up the body. The proliferative and developmental potential of human ES cells promises an essentially unlimited supply of specific cell types for basic research and transplantation therapies for diseases ranging from heart disease to Parkinson's disease to leukaemia (Richards, 1992).

Embryonic stem cells are derived from embryos at a developmental stage before the time that implantation would normally occur in the uterus. Fertilization normally occur in the oviduct, and during the next few days, a series of cleavage divisions occur as the embryo travels down the oviduct and into the uterus (Robinton, 2012). Each of the cells (blastomeres) of these cleavage-stage embryos are undifferentiated, i.e., they do not look and act like the specialized cells of the adult, and the blastomeres are not yet committed to becoming any particular type if differentiated cell. Stem cells are pluripotent cells widely distributed in human tissues and organs having a significant role in human physiology. These cells are capable of renewing damaged and lost cells in various tissues/organs. The life starts from one hybridized cell; zygote an ultimate source for stem cell and most of the stem cells in zygote are multipotent. The embryonic layers endoderm, mesoderm, and ectoderm are key sources for multipotent stem cells differentiate into various tissues and organs (Sanes, 1989). During gestation period, the umbilical cord and cord blood cells are rich in stem cell also helping in growth and development of growing foetus. These cells are now preserved for future application. The cord blood preservation may help in curing disease using stem cells. The most important tissue in the human body in context with stem cell is bone marrow-rich in various kinds if stem cells acting as progenitor cells growth of red blood cells and white blood cells (Seki, 2010). Several vital human organs including brain, heart, lungs, kidney, and liver require a continuous supply of stem cells either natively and or from other tissues to maintain their structural and functional integrity. In case loss of such somatic stem cells due to infection and or any pathological condition growth and repair mechanism alter in greater extent affecting tissue/organ physiology (Shapiro, 2005). The cancer chemotherapy/ radiotherapy are one classical example where there is massive loss of normal cells along with tissue-specific stem cell primarily in bone marrow.

The liver is having a large scale of tissue regeneration. Similarly, cells in the hair follicle and cells in adipose tissue have higher cell potency to help tissue regeneration. The stem cells also regulate organogenesis and aging and hence the external supply of stem cell may reduce aging symptoms (Takahashi, 2006). There is increasing scientific reports and finding towards the physiological significance of stem cell, and hence stem cells may be used for cell replacement, for therapeutic interventions, and potentially to modify aging. The stem cell transplantation and stem cell therapies are common approach to supply stem cell to targeted tissues/organs. The ethical issue associated with embryonic stem cells and several other challenges forced the researcher to find an alternate for stem cell. The induced pluripotent cells (IPSCs) derived from stem cell engineering is growing concept to produced desired stem cell for clinical application (26). Induced pluripotent stem cells (also known as iPS cells or iPSCs) are type of pluripotent stem cells, commonly abbreviated as iPS cells or iPSCs are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of certain genes and transcription factors (Thomson, 1998). These transcription factors play a key role in determining the state of these cells and also highlight the fact that these somatic cells do preserve the same genetic information as early embryonic calls. The ability to induce cells in a pluripotent state was initially pioneered in 2006 using mouse fibroblasts and four transcription factors, Oct4, Sox2, Klf4, and c-Myc (Van Prang, 2002). These induced cells exhibit similar traits to those of embryonic stem cells (ESCs) but do not require the use of embryos. Some of the similarities between EDCs and iPSCs include pluripotency, morphology, self-renewal ability, a trait that implies that they can divide and replicate indefinitely, and gene expression. Several methods can produce the induced pluripotent cell, and two major mechanisms commonly used in are-

Reprogramming somatic cells to induced pluripotent stem cells is a critical and potentially time-intensive step in stem cell research. The stem cell programming allows producing various kinds of stem cells from somatic cells by assigning new and desired genes. The four major genes Sox2, Oct4, Klf4, and cMyc insertion into somatic cell turn it into a stem cell provided other nutrient and growth conditions. Here, molecular biology plays an integral role in inserting selected four genes changes phenotype of a somatic cell (Miyamoto, 2002). The location and orientation of selected genes in somatic cells to convert into a stem cell are also important. By comparing gene expression patterns between different ES cell lines and between ES cells and other cell types such as adult stem cells and differentiated cells, genes that are enriched in the ES cells have been. From precision genome editing and gene modification technologies to high-efficiency delivery systems, researchers have developed a broad range of solution to create the modified genes expression systems, and stable cell lines you need for research-from culturing cells to modification, the detection and analysis. The gene editing is one of most recent technology in molecular biology capable of doing changes at gene level without affection other genes (Manz, 2002). The gene editing allows us to change gene functioning by making changes at coding region and or regulatory region for a gene. Several approaches have been developed to introduce genetic elements randomly into the human ES cell genome, including electroporation, transfection with lipid-based reagents, and lentiviral vectors. Here, CRISPR/Cas is one of the latest technology in gene editing available and quite efficient. Gene editing also associated in negative regulation of gene and inhibiting its function, RNAi, small pieces of double stranded RNA (siRNA; small interfering RNA) are either chemically synthesized and introduced directly into cells, or expressed

from DNA vectors (Arber, 2003). Once inside the cells, the siRNA can lead to the degradation of the messenger RNA (mRNA), which contains the exact sequence as that of the siRNA. mRNA is the product of DNA transcription and normally can be translated into proteins. RNAi can work efficiently in somatic cells, and there has been some progress in applying this technology to human ES cells (Rossi, 2005). Stem cells have been applied in the treatment of serious diseases for more than 30 years. The FDA has approved five hematopoietic stem-cell products derived from umbilical cord blood for the treatment of blood and immunological diseases. The therapeutics use of the stem cell is vast and increasing rapidly due to their preliminary outcomes. The diseases where stem cell therapy has shown promising results are neurological disorders, cardiac disorders, inflammatory disorders, infectious diseases and wound healing (Quesenberry, 2010). The infertility management with stem cell therapy is emerged as a new arena in modern medicine and had shown promising results. The cancer management and stem cell therapy become complementary to each other.

Several clinical tails studies have been carried out and reported stem cell therapy quite successful. Here, stem cell therapy is applied especially to treat cancers which require high-dose chemotherapy within the scope of medical care. The patient's stem cells are extracted from bone marrow or peripheral blood before high-dose chemotherapy, stored temporarily and transplanted after the treatment to minimize the side effects of the aggressive chemotherapy and to support the regeneration of destroyed cells (Reddy, 2002). Several attempts also have been made on horses, dogs, and cats can benefit the development of stem cell treatments in veterinary medicine and can target a wide range of injuries and diseases such as myocardial infarction, stroke, tendon and ligament damage, osteoarthritis, osteochondritis and muscular dystrophy both in large animals, as well as human (Berrios, 2001). The use of stem cells therapies in orthopedics is quite successful and required as these physical abnormalities result in physical deformities. The cartilage damage in case autoimmune disorders including rheumatoid arthritis are prevailing (Becker, 1999), and till date, there is no cure.

The stem cells from the patients either bone marrow and or adipose tissue also blood can provide symptomatic relief as selected stem cell allow a growth of cartilage and retain physical movements. The stem cells have a significant impact on the management of eye disorders as well as damaged cornea can be repaired by selected stem cell therapy. Most important neurological disorders where neurons are permanently damaged and lost have only way to treat by stem cell therapies. Here both IPSCs and stem cells from other source are being used, and a few cares under clinical studies (Reddy, 1997). Similarly, lost beta cells play a crucial role in insulin production and several other hormones in carbohydrate metabolism can be cured by stem cell therapies. The blood cell formation, regrowing teeth, hair and skin growth and replacement can be done using selective stem cells (Colvin 2004). The tissue and organ transplantation have a great scope in clinical practice with the advancement of stem cells (Charles, 2012).

History and Mechanism

Cell culture is not a new technique in the scientific world, it was started way back 1885 with Roux, embryologist maintained chick embryo in warm saline for a few days and it was the first recorded example of successful explanation. Jolly in 1903 reported cell survival and cell division in *in vitro* using salamander leukocytes. In the year 1907 Ross Harrison developed the frog embryo tissue by cell entrapment and cell growth with clotted lymph fluid in a depression slide. The isolated tissue was suspended on the underside of a cover slip, which was sealed over a depression in microscope slide. Burrows from 1910 continued the development of this technique with the use of plasma clots for the efficient growth of cells from warm-blooded animals and also with matrix of insoluble protein provided the necessary anchor for cell growth, and nutrients were provided by the enclosed fluid. One of the major difficulties of this work was the maintenance of the cultures free from contamination. The difference in growth rates between animal and bacterial cells in such that a low-level contamination in an animal cell culture can quickly lead to bacterial overgrowth.

Alexis Carrel trained as a surgeon, introduced the 'Carrel flask' which facilities subculture under aseptic techniques to cell culture *In vitro,* but it was difficult to repeat and so the cell culture was not adopted as a routine laboratory technique until much later. In the year 1912, Carrel initiated chick embryo heart cells culture given the appropriate conditions, isolated cells could be cultured indefinitely and later he illustrated the cell growth by supplementation of embryo extracts and continuous new cells addition is the culture during medium replenishment. Hayflick and Moorhead in 1961 with his coworkers reported the finite capacity for growth of 'normal' cells. Trypsinization is the treatment of cells by the proteolytic enzymes trypsin to change their adhesiveness. By the year 1916 Rous and Jones used trypsin to free cells from tissue matrix and also subsequently used for the subculture of adherent cells and in 1950s, the technique of Trypsinization was exploited to produce homogenous cell strains (as opposed to tissue cultures which contain a mixture of cell types) and this marked the start of animal cell culture techniques. Cell culture medium from the 1940s onwards alleviated contamination problem, which by the addition of antibiotics, penicillin and streptomycin in medium containing the embryo extracts or animal blood serum greatly reduced the microbial contamination, by the use of laminar air flow cabinets, minimize the possibility of contamination by airborne microbes. This have been encouraged the widespread use of cell culture as a laboratory technique, particularly after the isolation of variety of cell types which showed good growth characteristics *In vitro*. Earle and Eagle's 1950s focused work on development of chemically defined media with the chemically transformed mouse L cells and the human carcinoma cell line, HeLa.

Significance gap in Research

Is it possible to regenerate the brain of clinically dead? If it is curable, then patients were never brain dead in the first place.A person is confirmed as being dead when their brain stem function is permanently lost.However, although brain dead humans are technically no longer alive, their bodies can often still circulate blood, digest food, excrete waste, balance hormones, grow, sexually mature, heal wounds, spike a fever, and gestate and deliver a baby.Regenerative medicine is emerging with great interest and hope from patients, industry, academia, and medical professionals. Cartilage regeneration, restoration, or repair is one of the prime targets that remains

largely unsolved, and many believe that regenerative medicine can possibly deliver solutions that can be widely used to address the current gap(s) in treatment (J Clin Orthop Trauma, 2016).

Ideas where Research go Next

Dead bodies can provide organs for transplants, now they might become a source of stem cells too. Huge numbers of stem cells can still be mined from bone marrow five days after death to be potentially used in a variety of life-saving treatments. Human bone marrow contains mesenchyme stem cells, which can develop into bone, cartilage, fat and other cell types. MSCs can be transplanted and the type of cell they form depends on where they are injected. Cells injected into the heart, for example, can form healthy new tissue, a useful therapy for people with chronic heart condition. Stem cells can remain alive in human corpses for at least 17 days after death, researchers say. Stem cells give rise to all other cells in the body, a property that makes them extraordinarily valuable in potential therapies. These potent cells are often rare, only present in small numbers in tissue samples from patients and difficult to distinguish from other cell types in many cases. As such, scientists are investigating novel ways to procure stem cells and improve the viability of the ones they can get.Past research had suggested that stem cells could actually survive in up to 2-day-old cadavers, but researchers had thought that dead bodies would be poor homes for any cells, lacking the oxygen and nutrients the body's cells need to stay alive. Nevertheless, histologist and neuropathologist Fabrice Chrétien at the Pasteur Institute in Paris and his colleagues were curious to see how long stem cells might keep ticking after a person died. The researchers only had access to remains 17 days old, suggesting they have not yet seen the limits that stem cells can reach. "Maybe they can also resist longer," Chrétien told Live Science (Charles, 2012). Research on stem cells continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of the most of the fascinating areas of contemporary biology, but as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

Current Debate

In the United States, Europe, Australia, and India the regulation of regenerative based treatments has become a big debate.Doctors determine brain death by checking whether the patient's pupils react to light, whether he responds to pain, and if his body tries to breathe or has retained any other vital function of the brain stem, the part most resilient to injury. When the heart stops the blood supply to the brain is quickly cut off – and in operating theaters this moment would be recorded as the official time of death.But studies show that the dead person's mind and consciousness continue to work, at least for a short time – meaning the deceased can recognize their own death.Indeed there is some evidence to suggest the 'dead person' may even hear their own death being announced as they lie on the operating theatre table (LARA DEAUVILLE). The current prospects of stem cells are are highly promising and these cells are using for neurological disorders, cardiac dis order, cancer management, neonatal abnormalities and various progressive degenerative disorders as ell. The stem cell engineering and genome editing technologies are growing and having a positive impact on stem cell biology for clinical outcomes.There are increasing number of human diseases and disorders failed to find a cure for conventional medicine need integration with stem cell biology for complete cure. The major challenge in the stem cell biology is their collection itself. The cutting-edge molecular biology techniques ate competent in harvesting stem cells, but their efficiency is quite low and requires a repeated cell harvesting. The stem cell purification and processing is an expensive research exercise as well. The stem cell culture and maintenance are quite expensive and need a large laboratory setup and storage facility (Cerny, 2002). The stem cells are much prone to contamination and are short-lived. The handling of stem cell is quite difficult; required specialized culture media and consumables enhanced research cost. Based on cell morphology and molecular marker we can only identify stem cell which requires further cutting-edge medical molecular biology skills and research setup.

Though the stem cells have great potential in several clinical applications their handling start from harvesting, culture, storage and dispensing is complex (Habibian, 1998). The genetic manipulations in stem cells are time-consuming as their grown time is quite slow. For example; E. coli doubles in 20 min while a human cell needs almost 24 hours to divide. The complex eukaryotic cellular and subcellular environment of stem cell is comparative complex to study for desired changes. The stem cell research needs ethical approval for its use in research and clinical applications. All these facts demonstrate stem cells arequite challenging over other types of cells at research and application level. Apart from these challenges at the research level, there are several ethical concerns as well with stem cell. The human embryo is a most competent source of all kinds of stem cells including totipotent, pluripotent and multipotent. There are other sources as well for stem cell harvesting, but the yield of stem cell is quite low. As a result, a human embryo is an ideal choice as a source of stem cell. The key ethical issues concern the destruction of human embryos for stem cell derivation. Because the human embryo is a human life with moral value justifying its protection, the extraction of embryonic stem cells is unethical (43). In the course of stem cell harvesting, there are medical risks of oocyte retrieval include ovarian hyper stimulation syndrome, bleeding, infection, and complications of anesthesia. The genetic manipulations to wild types of cells including stem cells called as unethical as we are intensely creating a change that is irreversible.

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