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Stem Cell Research: Efficacy, Legal Framework and its Patentability Issue

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Abstract

Stem cells are the unspecialised cells that have the exceptional ability to renew themselves through cell division and under certain natural or experimental conditions; they can be induced to become specialised cell types. Generally, adult stem cells, embryonic stem cells, and induced stem cells are popular amongst various stem cells. Of these stem cells, no considerable ethical concern has been raised against the use of Adult Stem Cell; however, Embryonic Stem cell has been under the controversy from the very beginning. This is because embryonic stem cells are derived by destroying the embryo, which some scholars considered as equivalent to the human being. Thus, destroying an embryo is similar to the killing of a human being. Simultaneously, these stem cells have a therapeutic use, and some scholars also presume that treatment of diseases like Diabetes, Cancer, and hurt is possible through stem cells. To understand Stem Cell Research, this article discusses first in part I about stem cell research and types of stem cells. In part II, we will discuss the importance of stem cell research with some case studies and possibilities of the therapeutic use of stem cell for the COVID-19. In part III, we will analyse the ethical, moral, religious, and other issues against the use of stem cell research. In part IV, we will analyse the existing legal framework and patentability of stem cells in the UK, USA, and India. Finally, in part V, we will discuss findings and concludes. In this paper, the researcher has applied the doctrinal method of research based on the secondary data available on the various locations of the internet, books, and case laws.

Keywords: *Specialized cell, Embryo, Therapeutic use, COVID-19 and Patentability*

Introduction

Stem-cell research is the field of research that analyses the characteristics of stem cells and their possible use in science and medicine. The stem cells being a source of all the tissues, assist in our understanding of the healthy and diseased body's development and homeostasis. The human body comprises different types of cells, and these "cells are th*e smallest basic structural, functional, and biological unit of all known organisms"*. Simply put, these cells are responsible for structural growth and the body's biological functioning.

Stem cells are the unspecialised cells that have the exceptional ability to evolve into many different cell types of these cells. Under the appropriate circumstance in the body or a laboratory, stem cells break down to form more new cells called daughter cells. These daughter cells split into new stem cells or specialised cells like blood cells, bone cells, or brain cells. This process of splitting into a specialised cell type is called differentiation. These stem cells frequently divide to renew and repair existing tissues. For instance, in some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. However, in other organs such as the pancreas and the heart, stem cells only divide under special conditions.

Stem cells sometimes are referred to as "undifferentiated" cells because they have not yet committed to a developmental path that will form a specific tissue or organ. Thus in this way, stem cells are distinct from other sets of cells in the body. The distinguishing characteristic of stem cell can be written as follows:

- they are unspecialised cells
- capable of renewing themselves through cell division, and
- under certain natural or experimental conditions, they can be induced to become specialised cell types

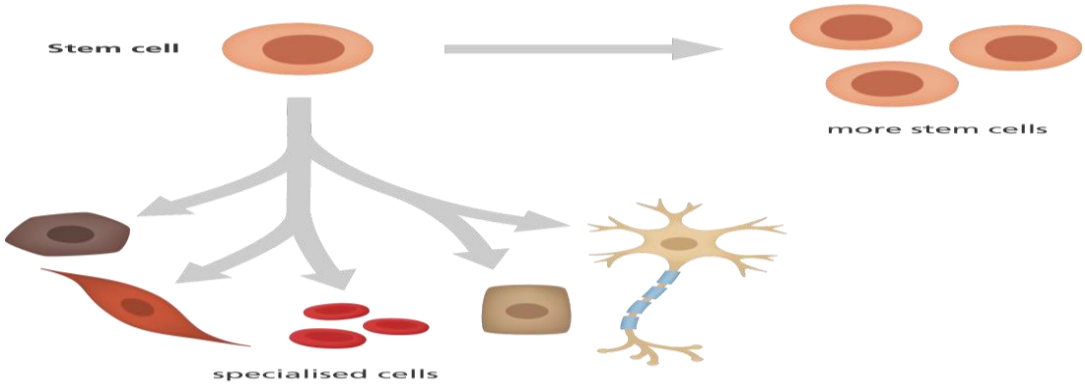

Fig. 01: Image showing stem cell can either become a new stem cell or specialised cell
Image credit: Genome Research Limited

Types of Stem Cells: Based on their nature (dividing capabilities) they can be categorised as-

S. No.	Types	Description	Example
1.	**Totipotent**	These are the stem cells that are cable of dividing and differentiating into cells of the whole organism. It has the highest differentiation potential and allows cells to form both embryo and extra-embryonic structures.	Blastomeres
2.	**Pluripotent**	These stem cells are cable of dividing and differentiating into any type of specialised cell structure, except, extra-embryonic structure.	Embryonic stem Cell
3.	**Multipotent**	These are the stem cells that are cable of dividing and differentiating into not all but most specialised cells. Thus it can be compared that it has a narrower scope than the Pluripotent.	Adult Stem Cell
4.	**Oligopotent**	These are the stem cells that are cable of dividing and differentiating into several selective specialised cells. These are even narrower than the Multipotent stem cells.	Myeloid stem cells
5.	**Unipotent**	These are the stem cells that are cable of dividing and differentiating into only one specialised cell. It has the narrowest differentiation capabilities. However, it has a special property of dividing repeatedly.	Neural stem cell

Table 02: Types of Stem Cells

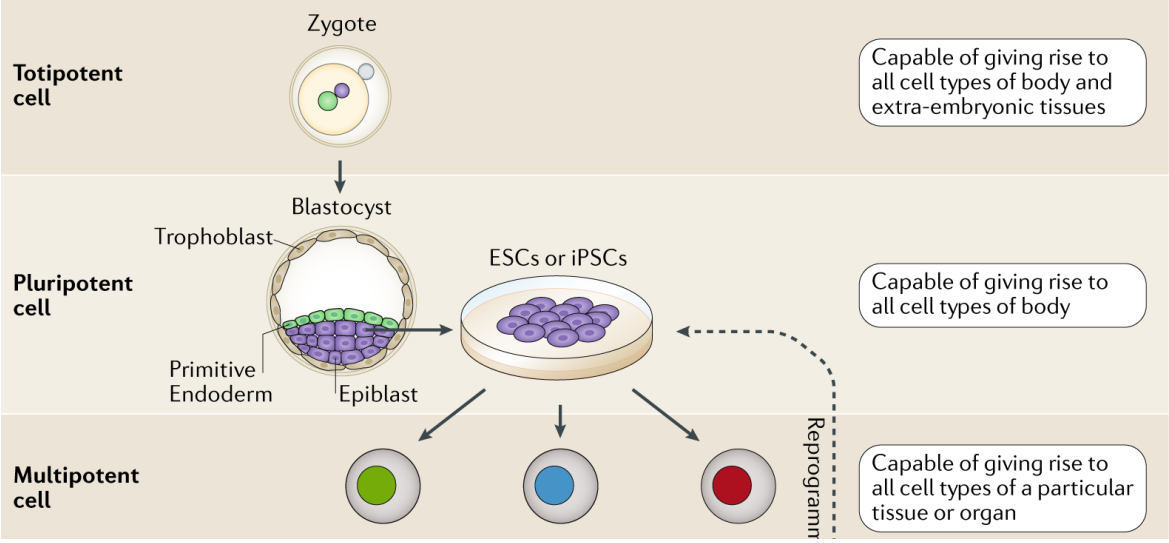

Fig. 02: Image explaining working of Totipotent, Pluripotent and Multipotent Stem Cell

Image source: Nature Reviews Genetics

The three main stem cells which are frequently used are as follows-

- **Adult stem cells (ASCs)**
- **Embryonic stem cells (ESCs), and**
- **Induced pluripotent stem cells (IPSCs).**

1. Adult Stem Cells (ASCs)

Adult stem cells are "undifferentiated cells found living within specific differentiated tissues in our bodies that can renew themselves or generate new cells that can replenish dead or damaged tissue." They were also called **Somatic Stem Cells**. Adult stem cells are multipotent and thus can generate not all but the majority of the specialised cells. In 1948, the first adult stem cells were obtained and utilised for blood production. Further, in 1968, this procedure was developed, and the adult bone marrow cells for the first time were used in clinical therapies for blood disease. Adult stem cells are usually deficient in native tissues, which have turned into a situation where it was challenging to study and obtain adult stem cells for research purposes. One dispute still prevails regarding developing adult stem cells because it only generates the cell in which it resides.

In contrast, others say that it can generate other tissues as well as those where it resides. Adult stem cells have been identified in many organs and tissues, including the brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. Scientists

continuously worked on adult stem cells to grow in large quantities and manipulate them to generate specific cell types to utilise for injury or diseases. Some examples of potential treatments include regenerating bone using cells derived from bone marrow stroma, developing insulin-producing cells for type 1diabetes, and repairing damaged heart muscle following a heart attack with cardiac muscle cells. As for as ethical, religious, or any issue is concerned, adult stem cells are free from it, and no significant concerns have been raised.

2. Embryonic stem cells (ESCs)

Embryonic stem cells are derived from the inner cell mass of an embryo that has been fertilised *in vitro* and donated for research purposes following informed consent. The embryo following 3-5 days of fertilisation and before implantation is called a blastocyst is containing an inner cell mass capable of generating all the specialised tissues that make up the human body. It is noted that embryonic stem cells are not derived from eggs fertilised in a woman's body. Embryonic stem cells are pluripotent and thus can generate any type of specialised cells. In 1994, the first human embryonic stem cells were derived from the old world monkey species called Rhesus Macaque. It brings an evolutionary change in the field of biotechnology which encourages the scientist to give more commitment. As a result, in 2009, the first clinical trials with human embryonic stem cells were instated. This development led to therapeutic cloning by human embryonic stem cells in 2014, and gene-editing technology was applied to human embryonic stem cells in 2015.

3. Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) are stem cells that are obtained in the laboratory through embryonic and adult stem cells. The resultant induced pluripotent stem cells are created to follow the properties of embryonic stem cells and are thus pluripotent. However, both induced and embryonic stem cells differ in clinically significant ways. The first iPSCs were created in the Mouse in 2006, and human iPSCs were first developed in 2007.

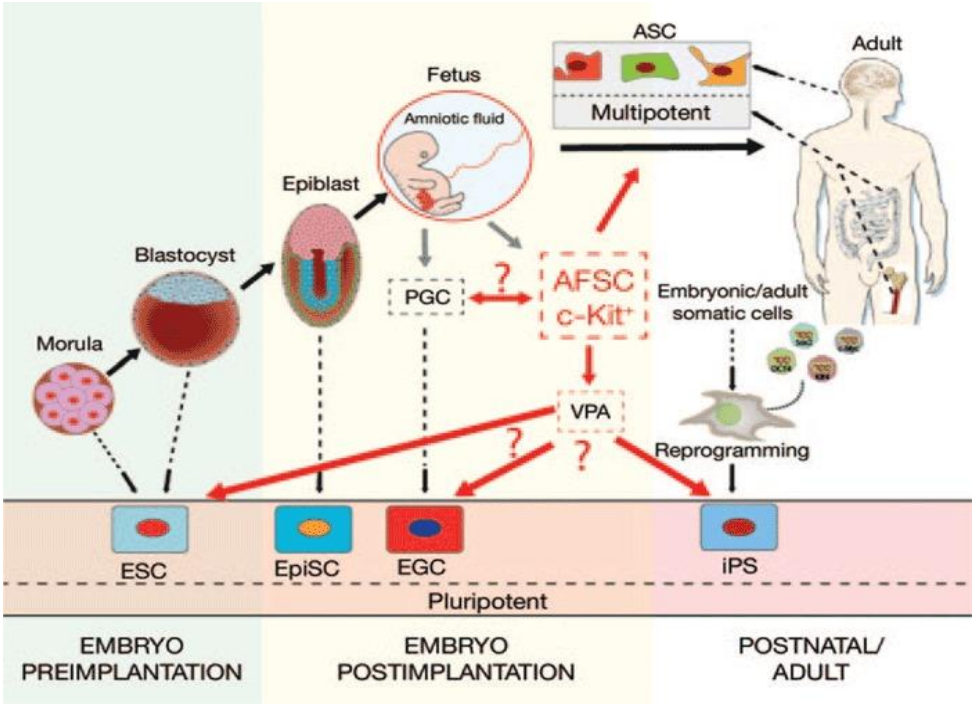

Fig. 03: Image showing the development of Embryonic, Adult and Induced Stem Cell

Image source: Research Gate

Research Methodology

In this paper, the researcher has applied the doctrinal method of research based on the secondary data available on the various location of the internet, books and case laws. The facts of cases are taken from various website. The other relevant information and the comparison of the same have been a reasonable inference collected from various other sources and an opinion by the different scholars, judges academicians.

Importance of Stem Cell Research

The primary and important objective of stem cell research is to understand the stem cell properties better. This will ultimately lead to the knowledge and behaviour of stem cells. Through stem cell research, only we can understand how to control their behavioural pattern to be turned into any specialised cell, for example, brain cells or heart cells. Some of the possible uses of stem cell research can be pointed out as follows:

S. No.	Uses of Stem Cell Research
1.	to understand human development
2.	to understand the behavioral pattern of diseases like cancer
3.	to provide specialised cell to repair or replace damaged cell
4.	to identify new treatment and drugs for the diseases like cancer through stem cells **(Therapeutic use of stem cell)**
5.	to replicate new cell, tissues, or organs **(Cloning)**
6.	to assist other research investigation in **Clinical Trails**

Table 03: Uses of Stem Cell Research

The three main uses or benefits of stem cell research viz. therapeutic use of stem cell, cloning, and a clinical trial will be discussed in brief in the following sections.

1. Stem Cell Therapy

From the last ten years, the therapeutic use of stem cells has gained recognition worldwide. The scholars presume that stem cell therapy can fully fill the shortcomings in human medical therapies for the treatment of diseases like Diabetes, Cancer, Hurt Diseases, etc. In this hope, there is continuous research on the therapeutic impact of stem cells. The following living examples can illustrate the progress in stem cell therapy.

S. No.	PARTS	Description
1.	**Teeth**	Prof. Pual Sharpe in London is working on a method to develop human teeth from stem cells to replace lost teeth. In animal studies, they have shown that embryonic and tissue stem cell populations can be identified that can all form tooth primordia that are themselves able to develop into complete teeth in the adult mouth.
2.	**Trachea**	Using a scaffold windpipe from a donor, a patient's own stem cells were used to re-grow the cellular part of the windpipe outside of the patient's body. The new windpipe was then transplanted into the patient.
3.	**Pancreas**	The insulin-producing beta-cells of the pancreas are destroyed in type I diabetes patients. To produce beta-cells in type I diabetes, patient research will

		transform embryonic stem cells into beta-cells to repair pancreatic function.
4.	**Blood/Immune system**	Stem cell therapy in bone marrow transplants has been used since the 1950s to treat immune disorders.
5.	**Brain**	The stem cell research on the efficacy of pluripotent stem cells is ongoing to treat Parkinson's disease in the human body. The research was started after successful completion in Animal models.
6.	**Skin**	After the successful trial in mice to produce skin grafts, human trials are planned. This technique could help the patient with serious burns. The technique could potentially provide an unlimited supply of temporary skin for patients with large burns who are awaiting grafts of their own skin.

Table 04: Description of Therapy through Stem Cell

2. **Cloning**: It is the process of making an identical copy of an organism or cells. Cloning can be broadly divided into two categories, viz. Reproductive Cloning and Therapeutic Cloning. However, cloning of embryonic stem cells for therapeutic purposes tends to be converted into Reproductive Cloning, which is formally banned by most countries.
3. **Clinical Trial:** New clinical trials through stem cells are currently being tested to treat musculoskeletal abnormalities, cardiac disease, liver disease, autoimmune and metabolic disorders (amyloidosis), chronic inflammatory diseases (lupus) and other advanced cancers.

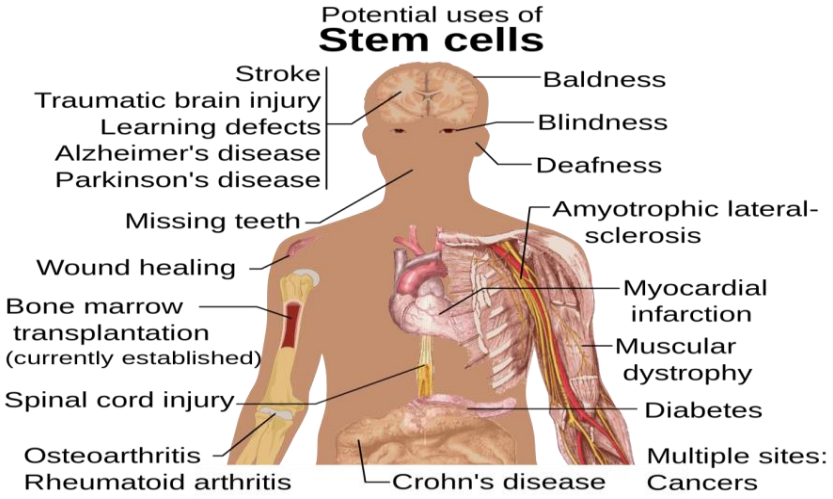

Fig. 04: Image showing potential uses of stem cells

Image Source: UNMC

Case Study
1. ***Stem cell therapy gets paraplegic Capt back on feet, Mumbai, India:*** Two years after he was shot at by an Afghan militant in Kashmir, Captain Manish Singh, who was left paraplegic by the injury, can walk again, thanks to 18-month stem cell treatment. Coupled with rehabilitation, Capt Singh, who could not even sit, is now mobile with the help of callipers.
2. Bihar's 1st stem cell therapy at AIIMS-P: AIIMS-Patna achieved a major feat on Wednesday by performing the first stem cell therapy in Bihar. A very rare experiment done in select hospitals of the country, stem cell therapy was performed on a Chhapra patient whose spinal cord has been damaged.
3. ***In Chennai, India, Doctors prescribe stem cell cure for tumours***: After extensively using stem cell therapy to treat leukemia, doctors are now pushing for using it to help cure solid tumours.

Table 05: Case Study

STEM CELL RESEARCH AND CORONAVIRUS DISEASE 2019 (COVID-19)
Currently, COVID-19 as a pandemic has caused unreasonable fear and led to unnecessary suffering and death worldwide. The Clinicians and researchers were engaged in finding a solution or treatment for the management of this Pandemic. Recently, Mesenchymal stem cells (MSCs) have introduced one of the therapeutic approaches for use in the treatment of COVID-19. An immunomodulatory and anti-inflammatory property of MSCs – Multipotent Stem Cells has attracted the mind of the researcher and scientist for the treatment of Coronavirus through MSCs. However, currently, there are no approved MSC-based approaches for the prevention and/or treatment of COVID-19 patients but clinical trials ongoing.

Table 06: COVID 19 and Stem Cell

Issues/Concern

There are ethical, moral, religious, political, and some other general arguments for and against stem cell research and the use of stem cells for therapeutic research, cloning, and clinical trial. Generally, no considerable ethical concern has been raised against the use of Adult Stem Cell; however, Embryonic Stem cell has been under the controversy from the very beginning. The major arguments put against and for stem cell research are discussed here one by one.

1. Ethical Issues

Ethical issues can be understood from the utilitarian and deontological ethical philosophy. According to Utilitarian philosophy, the consequences of stem cell utilisation should be assessed using the benefit to harm ratio as a measure to accept or reject the new technology. That means the scholars of utilitarianism believed that Embryo is only a spare part of the body and can replace lost or damaged cells in the body. They seem an ethically acceptable trade-off to destroy embryos for the prospect of saving human lives or curing diseases.

On the other hand, deontological philosophers believe that using stem cells is justified if the action is itself right rather than thinking of the consequences of the actions. The deontological thinkers give a picture to think about using Embryonic Cell, that is, whether the use of the Embryonic Cell is right in itself, which destroys an Embryo in its action. This idea of deontology raises ethical opposition against the use of Stem Cells.

2. Moral Issue

The Embryonic stem cell must be extracted from the destruction inner cell mass of the Blastocyst (embryo) which is formed after 3-8 days of fertilisation. Some Deontological thinkers believed that the destruction of human embryos is morally equivalent to killing a human being. Some of the views that embryo is also a human being, considering its capabilities to develop into a human being. Some of the views that it is not as a human being and must not be attributed to any moral status. Some people agreed with both the above views and develop a new viewpoint that embryo are more than cells but less than persons. This view articulates that Blastocyst (embryo) is entitled to be respected as human beings, but not the same as fully developed human beings. According to this moral argument, the moral status of a human embryo gradually increases through its development in the uterus. At the point of birth, it is entitled to enjoy the full rights of human beings (United Nations Educational, Scientific, and Cultural Organization, 2004).

Another moral argument based on the stages of human development is that human develops under various stages. These stages include fertilisation, the formation of cleavage, Blastocyst formation, gastrulation, and organogenesis. The primitive streak occurs at the gastrulation stage, where the embryo gets its unique entity. Before this stage, embryos can split and produce two or more embryos; however, after the development of the primitive streak, the embryo is a unique entity. Given this fact, many believe that individuality starts at this point; hence the embryo can be used for research prior to this stage, up to 14 days of development (DeWert & Mummery, 2003).

Illustration:
1. "*To illustrate the point, in Edinburgh, late-night walking tours of the Old Town feature among their scary tales the deeds of Burke and Hare in the early nineteenth century, who murdered people and sold their bodies as anatomical specimens to the medical school. Most people would recoil at the idea of killing another human being in cold blood to provide spare parts or cells for another. Yet, some people consider that this is what we are doing if we allow the use of an early embryo to provide stem cells for replacement therapy because, in terms of its moral status, the embryo is as much a human being as a new-born baby." [Stem cells science and ethics by Dr Karen Devine, 2010]*

Table 07: Illustration as to Moral Issue regarding Use of Embryo

3. Religious Issue

Arguments were also made based on religions. According to Jewish thinkers, a human embryo is not treated as religious until the sixteen weeks of pregnancy. Consequently, research on stem cells through human embryo is allowed under this period. According to Christian views, the embryo has personhood from the time of conception only. According to Islamic views, the use of stem cells must be based on the utilitarian approach but with certain limitations, for instance, they are in support of cloning embryo stem cells for therapeutic purposes but at the same time, they are against the use of stem cell for reproductive cloning. It is important to note that even in the same religion, there are diverse views on using stem cells from destroying an embryo. For instance, in Islam, a group of people whose view is based on stages of development structure, some of the view that personhood would be considered after the complete development of human beings.

4. Other Issues

Apart from moral, ethical and religious issues, some other social and psychological issues must also be considered. It was argued that couples undergoing the physically and psychologically stressful process of infertility treatment might not be in the best environment to carefully assess the implications of donating their embryos or gametes for research purposes. It is when medical companies and industries are optimistic about the future of stem cell research, misinformed about stem cells, their potentials, their sources, uses, and harms to the donors. So obtaining free consent is problematic. Further, it also poses a threat to donor privacy.

The social issue may consider the insufficient understanding of the aim of the research amongst people who may donate the embryo. Some questioned whether the study was for the right purposes or not. Another issue is pertaining to the cloning of embryo stem cells for therapeutic purposes. It has consistently been argued that allowing cloning of embryonic cells for therapeutic research may give rise to reproductive cloning.

Case Study:
1. *"Risks of stem cell treatment, including tumors after stem cell injections (Amariglio et al., 2009, as cited in Lindvall, et al., 2004, 2006), drew attention to safety issues and the importance of medical and ethical standards before the clinical application of this new type of treatment."*

Table 08: Case Study

Existing Legal Framework in the UK, USA, and India

1. The United Kingdom

The debate on moral, ethical, and religious value ends up in the United Kingdom with the Human Fertilisation and Embryology Act 1999. The Act allows the use of an embryo for research purposes until 14 days of fertilisation. The research work can be carried out only after taking a license for the same purposes from authority established under the Act. The Act also made it legal to clone embryo for research purposes. The Human Fertilisation and Embryology Authority is a statutory supervisory body established to issue licenses to laboratories that are taking up research work on embryo and checking proper compliance of the rules and regulation under the Act. However, the Act itself underlines certain conditions before applying for the license. For example, embryos must not be used or kept outside the human body at a stage of development beyond 14 days. They must be shown that it is necessary or desirable to use embryos to achieve the research aims. In 2001, Act was amended with regulation allowing embryo research for certain other purposes, including understating the development of an embryo and treating serious diseases. The UK has also passed the Human Reproductive Cloning Act 2002, which bans cloning of embryos for reproductive purposes. In 2008 the HFEA was due to merge with the Human Tissue Authority, a statutory body to be set up under the Human Tissue Act 2004 provisions to create a new authority called the Regulatory Authority for Tissue and Embryos (RATE).

Patentability of Stem Cell: Having a very conservative scope of stem cell and moral requirement for patentability in the United Kingdom, the directive issued by the patent office reveals that human embryos

for industrial or commercial purposes are not patentable. The UK Patent Office further distinguished between pluripotent cells and totipotent cells and held that pluripotent stem cells are patentable while totipotent stem cells are not.

2. The United States of America

There is no federal law on the regulation of stem cells in the United States. As a result, it has never been banned but has a restriction on funding for stem cell research which was regulated from time to time. For instance, former President George W. Bush permitted federal funding for embryonic stem (ES) cell research only if the stem cells were obtained from a limited number of previously existing stem cell lines. The scope was further extended by another executive order of President Barack Obama in 2009 by permitting the use of ES cells other than those obtained from the previously designated stem cell lines. In the absence of any federal legislation, however, individual states are free to go their own way. Several – most notably California – have pledged large sums of money for ES cell research.

Patentability of Stem Cell: In the US, despite of conflict for funding to stem cell research, US Patent Law allows that stem cells and methods of making or using stem cells can be patentable. This is because US patent law has no requirement of morality for patentability.

3. India

In India, guidelines for stem cell research began to emerge in 2000 after some false and controversial claims made by Doctors and Hospital regarding treatment through stem cell. For instance, the case of Lifeline Hospital Chennai, where they claimed that an injection of stem cells can help "improve nerve function" following spinal cord injury. However, there is no clinical evidence that this is yet possible.

To ensure ethical and good quality of stem cell research, the Indian Council of Medical Research (ICMR) had for the first time issued a guideline in 2007. Certain shortcomings were pointed out by many scholars from time to time. As a result, in 2017, the Indian Council of Medical Research and the Department of Biotechnology issued new guidelines as National Guidelines for Stem Cell Research (NGSCR) 2017.

Important Features of the NGSCR Guidelines 2017

1. Stem cell research has been classified into three broad categories as:

a) Permissible Stem Cell Research: allowed establishment of new embryonic stem cell/induced pluripotent stem cell (iPSC) lines

b) Restrictive Stem Cell Research: Research involving human preimplantation embryos processed by *in vitro* fertilisation (IVF)/intracytoplasmic sperm injection/somatic cell nuclear transfer to derive ESC lines

c) Prohibited Stem Cell Research: Research involving human germline gene therapy and reproductive cloning studies human embryos beyond 14 days of fertilisation.

2. Three levels of manipulations are created for stem cell research viz. Minimal, Substantial and Major

3. Derivation of new human embryonic stem cells (hESCs) or iPSC lines from human embryonic or somatic cells, respectively, shall adhere to the conditions for gamete, embryo, and somatic cell donation, and with prior approval of IC-SCR and IEC.

4. The guidelines do not apply to research using (i) nonhuman stem cells and their derivatives; (ii) hematopoietic stem cells (where the standard of medical care has been established), and (iii) PRP and autologous chondrocyte/osteocytes implantation (categorised as "other cell-based applications")

Patentability of Stem Cell

The Indian Patent Act, 1970 under section 3(b) provides that 'an invention, the primary or intended use or commercial exploitation of which could be contrary public order or morality or which cause serious prejudice to human, animal or plant life or health or to the environment, are not inventions' and thus cannot be patented. Highlighting the ethical and moral grounds, it can be argued that stem cells cannot be patented in India. However, those arguments were not last lasting and keep on changes with time. For instance, though the draft manual of 2008 stated that embryonic stem cell patents are against public order and morality, the latest Manual published in 2011 does not mention anything about stem cell patentability. In the absence of any specific guidelines, stem cells can be considered patentable subject to Section 3 of the Act.

Conclusion

After discussing the meaning, objective, and importance of stem cell research, it cannot be denied the therapeutic use of stem cell research in the future. Even we have seen that Mesenchymal stem cells can be a promising treatment for COVID-19. We have seen that no major concern has been raised against the

Adult Stem Cell, but there has been a lot of controversy regarding using of Embryo Stem Cells. As far as the legislative framework is concerned, the UK has comprehensively dealt with it and enacted the HFA Act. But even then, there are certain loopholes, like the phrase 'necessary and desirable' for issuing a license is uncertain. The meaning of the phrase 'serious disease' is unclear.

On the other hand, the US has never come up with any federal law on stem cell research. If we analyse the condition in India, it is more balanced than the US but less than the UK. India has enacted NGSCR 2017 guideline, but even after comprehensive guidelines, there are uncertainties in the regulation of Stem Cell research. For instance, in Mr. Raghubir Singh and Another v. Union of India and Another, the court passed a ruling allowing a clinic in New Delhi to continue embryonic stem cell therapy for some of their patients even in the absence of approval under the New Drugs and Clinical Rules, 2019. There is still a need for a proper legislative framework that can regulate all possible uses of stem cell research in the future.

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