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Stem Cell Patentability: Legal Challenges

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Abstract: Stem cells are versatile cells capable of self-renewal and differentiation into different specialized cell types. Their immense potential has led to a surge in research and practical applications medicine. Patentability of the stem cells has been a subject of controversy, with concerns that restrictions on access to crucial technologies could hinder the translation of research into practical medical applications. It is a promising field that's rapidly advancing and has the potential to revolutionize modern medicine. The patentability of stem cells faces several legal challenges, including ethical, moral, and religious concerns, as well as difficulties in obtaining a patent license. Patent protection is crucial for driving innovation and commercial success in regenerative medicine and life sciences. This article examines the patentability restrictions and specific challenges associated with human stem cell patents in Europe and the United States.

Keywords: Stem cell; legal challenges; patentability; patents; USPTO; EPO

1. Introduction

Stem cells are group of specialized cells which are known for their capability to self-renewal and proliferation. Stem cells emerge from single cell and then develop into various types of cells and tissues as shown in figure 1(Kolios and Moodley 2013). Stem cells are present in both embryos and adult stages cells. Various steps are involved in the specialization. Unlike pluripotent stem cells, unipotent stem cells are not versatile as developmental potency is diminished with each stage of the differentiation. Totipotent stem cells are more versatile and have the potential to divide into any cell of the organism. Totipotency possesses the highest potential for differentiation and allows all cells to form extra-embryonic structures and embryos. (Zakrzewski et al. 2019)

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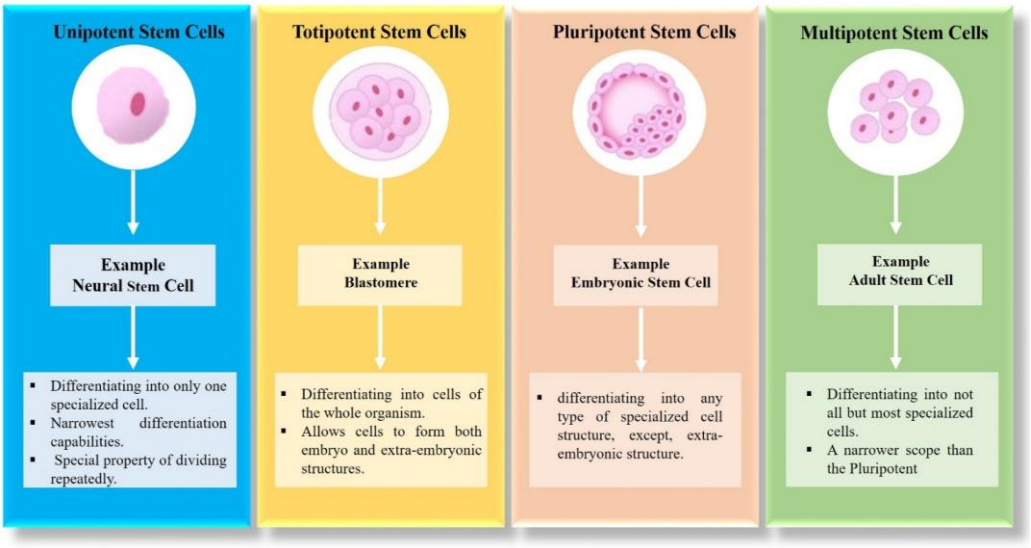

Figure 1. Different types of stem cells

Stem cell technology is the rapidly emerging and growing area of research with significant therapeutic potential. Particularly, human stem cells are the main focus of research as they hold the promising hope for clinical applications in future. Although, human stem cells possess the great potential, but, regulatory restrictions and ethical considerations have influenced/impacted the progress of regenerative medicine development and ultimately drug discovery. Although, the patents have been recognized as to protect the inventions of life sciences but still they are continuously facing the legal issues and challenges specifically human stem cells, especially human Embryonic Stem Cells (hESCs) (Wong and Mahalatchimy 2018).

Because of clinical effectiveness of the stem cells, a number of clinical trials exploring potential of the different lineages of stem cell in the wide range of therapeutical applications have been developed. These applications include mesenchymal stem cell therapy for Graft-versus-Host disease, hematopoietic stem cell transplantation for blood disorders and retinal pigment epithelium derived from induced pluripotent stem cells (iPSCs) to treat age related macular degeneration. Certain stem cell treatments are now being commercialized in Europe and America. These important findings raise queries regarding how such therapies can be effectively protected through Intellectual Property Rights (IPR) (Melchor et al. 2022).

There has been a long debate in both legal and scientific communities regarding patentability of the human embryonic stem cells. Moreover, recent rulings in U.S. courts have notably narrowed the criteria for patent eligibility in field of biotechnology. Consequences of current legal modification on stem cell patent eligibility criteria are evaluated in the European Union and the United States (Melchor et al. 2022).

This article mainly focuses on the standards and requirements for obtaining stem cell patents across different jurisdictions and the challenges encountered while submitting stem cell patents with their therapeutic uses. The authors goal is to give an overview of patent framework and exclusions in each jurisdiction, highlighting the particular difficulties faced by human stem cell-based patents. Furthermore, we will provide recommendations for addressing these challenges and adapting to the changing landscape.

1.1 Stem Cell Patents; Impact on Innovation and Research

Stem cell technology is a rapidly advancing field which brings together the expertise of geneticists, cell biologists and clinicians to offer promising treatments for the vast variety of diseases including both types of tumors. Stem cells are considered to be ideal for studying them in in-vitro as they efficiently survive and possess stable cell division in the culture (Fontes and Thomson 1999). Research on the adult, hematopoietic, multipotent and induced pluripotent stem cells has offered novel and valuable scientific discoveries, paved possibilities for the cell-based interventions and facilitated many innovative and novel ways for disease modeling. Stem cell research also faces many ethical challenges including acceptance of the animal research and protection of tissue donor's privacy of in the preclinical research. Stem cell research is also linked with other ethical challenges such as therapeutic misestimating or misconception, appropriate informed consent protocols, safety, side effects and potential costs of the interventions in their clinical translation (Assen et al. 2023). Although stem cell technology will transform the medical practices and has already demonstrated various basic mechanisms of diseases, but promise of the stem cell-based therapies still remains to be unrealized. Idea of stem cell is very old because first human embryonic stem cells were cultured by James Thomson in 1998 at University of Wisconsin. Scientists are very optimistic and realistic about the relevance of stem cells and their positive impact on human lives. The promising application of embryonic stem cells is cell replacement therapy, for treating injuries including stroke, Parkinson's disease and spinal cord trauma (Leventhal et al. 2012). Cell therapies, innovative scientific advancements, are increasingly integrated into medical practices by clinicians. These powerful tools are transforming modern medicine by addressing the growing need for effective treatments, especially for aging populations (Melchor et al. 2022).

The promising clinical outcomes of stem cell therapies have fueled extensive research, resulting in numerous clinical trials exploring the potential of different stem cell types for the vast range of therapeutic applications. It includes mesenchymal stem cell therapy for mesenchymal stem cell therapy for Graft-versus-Host disease (Li et al. 2022), hematopoietic stem cell transplantation for blood disorders (Duarte et al. 2019), retinal pigment epithelium derived from induced pluripotent stem cells for age related macular degeneration (Dehghan et al. 2022).

1.2 Stem Cell Patenting Eligibility Criteria

According to section 101 of patent act list, there are four categories which are patentable; novel and new procedure, machine, manufacturers and composition of the matter. However, there are three categories identified by the Supreme Court, which can't be patentable; laws of the nature, physical phenomenon and abstract ideas, although they fall within the categories of section 101 of patent list act as shown in figure 2 (Gott 1981).

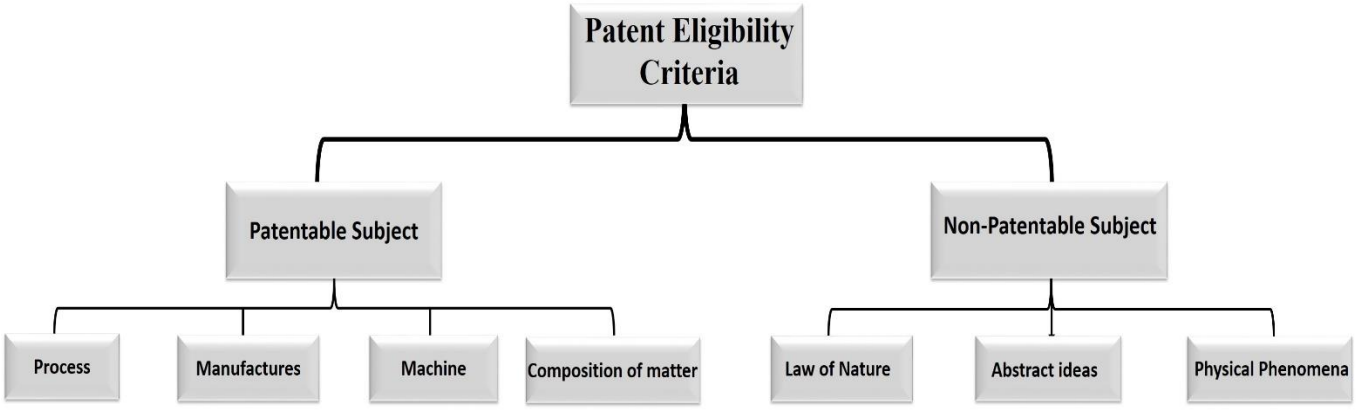

Figure 2. Eligibility criteria of patent filing

Although, there are no specific statutory exemptions for patents of stem cells. But, Leahy–Smith America Invents Act (AIA), Pub. L. 112-29, sec. 33(a), 125 Stat. 284, addressed this issue by prohibiting the patents on the claim involving human organisms. This acts states that:

"Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism".

The most significant patent change in the US has been the AIA since 1952. According to legislative history of the AIA, stem cells are eligible for patents but patents can't be issued for the claims which are directed to or cover human organism, exclusively human embryos (Davey et al. 2015; Fendrick and Zuhn 2015). It seems that morality clauses which exclude the patentability of human embryonic stem cells (hESCs) will be continued in the European Union (EU). The restrictions on the patentability of hESCs were considered to be the major hurdle in commercialization of hESCs in the Europe as compared to United States (Porter et al. 2006).

The relevance of the decision stemmed from Court's reasoning lies that anything which is made by man under the sun is eligible for patent filing and this rule broadly removes the restrictions on the subject matter eligibility and expands the scope of patents criteria. According to the legal framework by *Chakrabarty* and *In re Bergy*, stem cells have been determined as patentable subject matter. Consequently, USPTO has issued a broad range of the stem cell patents.

USPTO has issued a memorandum "Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, & Natural Products (or also known as *Myriad-Mayo* Guidance)" on March 4, 2014, after following the decision of Supreme Court on *Mayo* and *Myriad* (Fendrick and Zuhn 2015).

The *Myriad-Mayo* Guidance establishes the new protocols for patent examiners to use when evaluating whether patent claims meet the eligibility criteria or not. This new process of examination basically consists of three-steps analysis in which the examiners must address the following inquiries; (1) Does the claimed invention fall in the four categories of patent-eligibility criteria: procedure, machine, manufactures, or composition of the matter (2) Does the claimed subject relate to any judicial exceptions which is identified by Supreme Court in the *Diehr* (laws of the nature, physical phenomenon and abstract ideas)? (3) Does the whole claimed invention *significantly different* from the judicial exceptions? (Gordon 2014; Wales and Cartier 2015).

Therefore, future of stem cell and wide range of biotechnological subject patentability is still uncertain.

2. Challenges in Stem Cells Patentability

Stem cell research is an emerging field but it faces many challenges including restrictions of patent and intense lobbying by the life sciences. Patents may hinder innovations in the field of biomedical sciences by encouraging corporations for investing more in legal teams over researchers and resources. The patenting and commercialization of stem cells have raised unprecedented ethical, legal, and scientific challenges. The future of stem cell intellectual property and its effect on human health will be shaped by a complex interaction of technical, ethical, and legal considerations, with substantial implications across different countries and legal systems (Plomer et al. 2008). Patent challenges are persistent and do not indicate the fundamental flaw in patent. Major hurdle in patenting of stem cell in European markets is moral exclusions of embryonic stem cells issued by European Patent Convention (EPC) Directive 98/44/EC, which limits their commercial or industrial use. Researchers have identified the need for the establishment of International human embryonic stem cell registries and International stem cell banks which facilitate the scientists to get stem cells from repositories (Ilyas and Reports 2020). Here is the brief discussion on legal issues of patentability of stem cell in USA and Europe.

3. Challenges in Stem Cells Patentability in USA

3.1 Legal Framework in the USA

The United States has been relatively open to granting patents on the stem cell technologies, including human embryonic stem cells. The U.S. Patent and Trademark Office (USPTO) adopts a broad interpretation of the patent eligibility under 35 U.S.C. §101, which allows for patenting of "any new and useful process, machine, manufacture, or composition of matter."

3.2 Key Legal Issues

Patentability of hESCs: The USPTO has a history of granting patents for stem cell-related inventions, with the first hESC line patent issued in 1998 to the University of Wisconsin. However, ethical concerns are addressed through federal funding restrictions such as the Dickey-Wicker Amendment, which prohibits federal funding for research involving the destruction of human embryos. Recent Supreme Court rulings, including Mayo Collaborative Services v. Prometheus Laboratories and Association for Molecular Pathology V. Myriad Genetics, have impacted the patent eligibility landscape, particularly for natural products and biological inventions. Despite these rulings, stem cells remain patentable in the United States if they meet the criteria of novelty, non-obviousness, and utility (Minssen and Nilsson 2012).

Moreover, the USA patent system does not allow for the public or external review of pending patent applications. A business which infringes on filed patent or uses it without any valid license can be challenged in the court and declare it invalid patent by the court. In 2006, two public interest organizations, the New York Public Patent Foundation and the California Foundation for Taxpayer and Consumer Rights, launched a significant challenge against the patentability of stem cells. They submitted reexamination requests to the USPTO, contesting the validity of three patents by Wisconsin Alumni Research Foundation (WARF) concerning embryonic stem cells (Fendrick and Zuhn 2015).

First WARF patent which was issued in December 1998, broadly claimed primate embryonic stem cells. A second patent, issued in March 2001, made similar claims, specifically focusing on human embryonic stem cells. Third patent described method for proliferation of hES cells in absence of growth factor LIF. These patents were remarkably broad, claiming ownership of all hES cell lines having specific characteristics and methods for their production. The composition of matter claims was particularly significant, as they encompassed any process involved in creating hES cell lines. While the outcome of reexaminations is unpredictable, WARF had reason to be optimistic. Most reexaminations result in the patent being upheld (Golden 2010).

3.3 Legal Framework in the Europe

Compared to the United States, Europe's approach to stem cell patents, especially under the European Patent Convention (EPC) and Directive 98/44/EC (Biotech Directive), is more restrictive due to its focus on ethical considerations.

3.4 Key Legal Issues

Under Article 53(a) of the European Patent Convention (EPC), patents cannot be granted for inventions that are considered contrary to public policy or morality. This explicitly prohibits patents involving the use of human embryos for industrial or commercial purposes. The European Court of Justice (ECJ) ruled in the Brüstle Case (C-34/10) of 2011 that processes involving the destruction of human embryos were not patentable, significantly limiting hESC patents in Europe. However, later rulings, such as the International Stem Cell Corporation V. Comptroller General of Patents case (2014), clarified that hESCs derived without destroying embryos (e.g., through parthenogenesis) could be patentable. Despite the European Patent Office (EPO) having a unified patent system, individual European countries, like Germany, have their own regulations. Some countries, such as Sweden and the UK, have more favorable policies towards stem cell research (Spranger 2012).

In 1998, the EU adopted the Directive on Biotechnological Inventions with the aim of standardizing patent rules among its member states. It is composed of two Articles: Article 5 of this directive prohibits patenting of the human body at various stages of development, while Article 6 excludes inventions contrary to public order or morality. This includes human cloning, germline genetic modification, and commercial or industrial use of human embryos. The European Patent Convention (EPC) of 1973 streamlined the patent application process by providing a uniform examination and granting procedure. Thus, the advantages of filing with the EPO depend on the reliability of patent protection under national laws, particularly in the contentious area of moral exclusions. The European Court of Justice has the power to assess whether national patent laws align with the EU Directive. Applicants who choose to file directly with national patent offices may bypass legal complexities and potentially expedite the process of securing patent protection (Bonetta 2008; Sheard 2014). However, patents granted by the European Patent Office (EPO) are still subject to national laws.

3.5 License to Research

Commercialization of the stem cell therapeutics are affected by availability and cost of license. Potential infringer should obtain a valid license of patents or avoid to use the patented technology. There exist no essential licensing provisions in United States, so that patentees /applicants patentees have the discretion to grant or withhold licenses. Financial incentives motivate patentees to grant licenses for work that doesn't directly compete with their own business. Financial incentives also motivate the patentees to set reasonable licensing costs for maximizing market for their patented technology. A poorly designed licensing strategy may hinder the advancement of the markets and technology. Some people have blamed the WARF of using this strategy but in reality these accusations may be driven by more emotions than the fact. Patentees who adopt a forceful licensing strategy, a form of inefficiency, may find their negotiating position weakened by a recent U.S. Supreme Court ruling. Ultimately, it should be kept in mind that that any commercial endeavor or research should have multiple licenses from different entities (Spalding and Simkin 2007). Different patents have already been filed as shown in table 1.

Table 1. List of active and published patents on stem cells from 2014-2024.

Sr#	Patent Number	Publication Date	Owner/Assignee	References
1-	US11980641B2	2024-05-14	Harvard College	(Chen et al. 2019)
2-	US11891623B2	2024-02-06	Accelerated Biosciences Corp	(Lee et al. 2017)
3-	AU2021282533B2	2024-08-15	Editas Medicine Inc	(Gori 2022)
4-	US11821006B2	2023-11-21	CellResearch Corp Pte Ltd	(Phan 2021)
5-	AU2021245259B2	2023-10-05	Janssen Biotech Inc	(Rezania 2019)
6-	AU2021266324B2	2023-06-08	Viacyte Inc	(Agulnick 2014)
7-	AU2020264375B2	2023-05-25	Dan S. KaufmanDavid A. Knorr	(Kaufman and Knorr 2016)
8-	AU2019222550B2	2023-01-25	Kite Pharma Inc	(Gschweng et al. 2021)
9-	US11795436B2	2023-10-24	Agency for Science Technology and Research Singapore National University of Singapore	(Yuanyu et al. 2020)
10-	US11723930B2	2023-08-15	Celularity Inc	(Edinger et al. 2013)
11-	AU2020201856B2	2022-07-14	Rutgers State University of New Jersey	(Shi et al. 2015)
12-	US11371022B2	2022-06-28	Harvard College Harvard University	(Park et al. 2022)

13-	US11332718B2	2022-05-17	University of Georgia Research Foundation Inc UGARF	(Stice et al. 2014)
14-	US11168302B2	2021-11-09	Clavistherapeutics Inc	(Park & Kim 2021)
15-	US11136548B2	2021-10-05	Whitehead Institute for Biomedical Research	(Muffat et al. 2021)
16-	US10842826B2	2020-11-24	University of Connecticut Imstem Biotechnology Inc	(Wang and Xu 2017)
17-	US10711244B2	2020-07-14	Max Planck Gesellschaft zur Foerderung der Wissenschaften eV	(Schoeler et al. 2015)
18-	AU2017216594B2	2020-01-23	Tsuneo KIDO	(Tsuneo 2015)
19-	US10570369B2	2020-02-25	Ramot at Tel Aviv University Ltd	(Pitaru 2020)
20-	AU2018202125B2	2020-09-17	Lineage Cell Therapeutics Inc	(West and Chapman 2017)
21-	US10751373B2	2020-08-25	Childrens Medical Center Corp	(Fiorina 2019)
22-	US10377989B2	2019-08-13	Janssen Biotech Inc	(Fryer et al. 2019)
23-	US10329534B2	2019-06-25	Janssen Biotech Inc	(Karanu and Rezania 2019)
24-	US10105396B2	2018-10-23	Temple Therapeutics Inc Texas A&M University System	(Prockop et al. 2017)
25-	US10030057B2	2018-07-24	General Hospital Corp	(Shah 2018)
26-	US9644238B2	2017-05-09	AUTOLOGOUS REGENERATION LLC	(Anversa et al. 2017)
27-	US9803177B2	2017-10-31	Childrens Medical Center Corp	(Rossi and Warren 2017)
28-	US9804151B2	2017-10-31	Geeta Shroff	(Shroff 2017)
29-	EP2820148B1	2017-07-26	McMaster University	(Bhatia et al. 2015)
30-	US9598670B2	2017-03-21	Sanford Burnham Prebys Medical Discovery Institute	(Terskikh and Bajpai 2017)
31-	US9487752B2	2016-11-08	Fujifilm Cellular Dynamics Inc	(Meyer et al. 2016)
32-	US8685730B2	2014-04-01	Wisconsin Alumni Research Foundation	(Odorico and Xu 2014)
33-	US8765470B2	2014-07-01	Fujifilm Cellular Dynamics Inc	(Thomson et al. 2014)

4. Challenges for Stem Cell Patents under WIPO Patent Framework

Legal protection of industrial designs and models varies, as texts have been provided for precautionary measures and civil and criminal protection, as follows:

4.1 International Ethical Concerns

Stem cell research offers significant promise for breakthroughs in regenerative medicine, tissue engineering, and tailored treatments (Cosson et al. 2015). However, obtaining intellectual property rights for stem cell innovations within the WIPO patent system is hindered by various challenges. One primary obstacles in patenting the stem cell technologies is ethical controversy surrounding human embryonic stem cells (hESCs). Because of ethical concerns surrounding destruction of human embryos, many European nations have been cautious about issuing patents for inventions that rely on hESCs (Bell 2010). European Court of Justice ruled in Brustle versus Greenpeace that patents are not permissible for inventions derived from hESCs when their extraction necessitates the destruction of embryos (Plomer 2012). As a global platform for intellectual property policy, WIPO must navigate the ethical complexities surrounding stem cell research while upholding a balanced approach that encourages innovation. Countries with more permissive regulations on the embryonic stem cell research, like United States may grant patents for technologies that are considered ethically problematic in other regions (Forsberg and Ethics 2012). An additional challenge in obtaining patents for stem cell technologies is the scientific complexity of the field. Due to the unique biological characteristics of stem cells, especially pluripotent stem cells, patent examiners often face difficulties in determining how to classify these innovations (Lorenz et al. 2013; Swami 2009).

4.2 Key Legal Issues

Many patent applications for stem cells are rejected due to a lack of novelty or obviousness, particularly when they involve standard procedures for isolating or culturing stem cells. Inventors in stem cell field face challenge of patent thickets, where multiple parties hold overlapping patents that can hinder future research and commercialization. This is particularly problematic in fields like regenerative medicine, where various entities own patents on different aspects of stem cell technologies, including methods of isolation, differentiation, and therapeutic applications (Colyvas et al. 2012; Wager and Miller 2018). Stem cell research exemplifies conflict between securing the intellectual property rights and ensuring access to life-saving therapies. The high costs of licensing patents can restrict treatment availability for those in need. WIPO has been engaged in discussions on how to balance IP protection with the broader objective of ensuring equitable access to new therapies, especially in alignment with the Sustainable Development Goals (SDGs) (Dahlin et al. 2015; Xue et al. 2020).

4.3 Intellectual Property and Patenting of Stem Cell

Therapy with stem cell has gained a lot attention due to its remarkable potential to cure variety of chronic diseases, degenerative conditions and great economic potential. Patents on stem cell differentiation procedures, intellectual properties and medical products developed from stem cell for cell and tissue therapy are very costly. There are many issues faced by the stem cell researchers especially Intellectual properties and patents. Stem cell researchers can develop cost effective stem cell therapies, scientific progress, and innovate for the benefit of patients in many countries (Loring and Campbell 2006). To acknowledge the original inventors of stem cell protocols and techniques, establish their reputations, and enable them to reap reasonable financial rewards, international patent barriers must be removed. Removing these barriers will be a decisive step for the advancement of the stem cell research (Kiatpongsan 2006; Zachariades 2013).

4.5 General Issues

Beyond the legal issues the ethical, moral, and religious concerns, social and psychological factors must also be considered (Resnik 2007).

Ethical issues in the patenting of stem cells in Europe

Stem cell research and usage of the stem cells in therapeutic studies, cloning and clinical trial are the subjects of various ethical, moral, political, religious and other arguments. Moral censuses are specifically increased and linked with human embryos at blastocyst stage. Regulatory and political controversies are generated on the work of human blastocyst when hES cells were firstly cultivated in the laboratories in 1998 (Robertson 2010), obstructing hES cell research in European Union (EU) (Hoppe and Denoon 2011). There are various perspective on the status of human embryos before the implantation and debate continues to be more intense (Andersson 2011; Condic et al. 2009).

4.6 Moral Issue

Moral status of the embryos is always debated whether they have the same status like children and adult human beings, having a right to the life which can't be sacrificed for the betterment of society. One perspective about the embryo is that it is just a cluster of cells which has no moral status than other human cells. This perspective suggests that there are very less, if there is any, ethical restrictions on research uses of the embryos (Singh 2008). Moral status of human embryo is seen to increase as it progresses in its development within the mother's womb, and upon birth, it is granted the full rights of a human being (Fendrick and Zuhn 2015).

5. Conclusions

The patenting and commercialization of human embryonic stem cells (hESCs) have created a unique and challenging situation with significant ethical, legal, and scientific implications. Despite facing limitations, research on human embryonic stem cells (hESCs) continues to advance. Different countries have varying cultural perspectives on use of stem cells, which can potentially influence the permissibility of patenting them. In the field of international stem cell research, ongoing review of specific criteria and actual practices is necessary to identify the challenges posed by existing proprietary systems. To foster greater coordination and promote stem cell science research, we must prioritize key research policies related to hESCs. The future of intellectual property of human embryonic stem cells (hESC) and its impact on the health of humans will be influenced by vast range of technical, ethical and legal considerations, varying across different countries and jurisdictions. While the field holds immense promise for improving human health, addressing the challenges posed by intellectual property rights is essential for realizing its full potential.

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