Is ethical, moral and social issues act as implicit limitations upon the Patenting of 'embryonic stem cell research and therapeutic cloning': Comparative study of USA, Europe and India

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Abstract

'Embryonic stem cell research and therapeutic cloning', the debate of the 21st century acquired the global attention due to the questions relating to ethical, moral and social issues raised against it. The modern patent law recognizes such inventions, which qualifies novelty, non-obviousness and utility. in case of embryonic stem cell research and therapeutic cloning, the creation of artificial embryo for developing clones babies triggered the controversy stating that the same is contrary to the rules of nature and set societal standards and values. The important question is whether any invention, which qualifies the patentability criteria, can operate in the society? Whether social standards and values act as an implicit limitation upon such inventions when there are no express limitations laid down? In order to solve the question, the article focused on the various judicial pronouncements laid down in different countries relating to embryonic stem cell research and therapeutic cloning.

1. Introduction

Whether human being succeeded in unfolding the secret of nature? The advent of embryonic stem cell research and therapeutic cloning methods expanded the human capacity to recreate the life. Through stem cell research, first scientists discovered how stem cells differentiate into the human body's cell types and later through embryonic stem cell research, cloning is made possible. The history shows that the mouse embryo is the first independently extracted embryonic stem cell at the University of Wiscosin.1 With this scientific breakthrough, it is now possible to develop therapies for so many diseases and debilities, including: neuron cells for Parkinson's, Alzheimer's, AIDS, and spinal cord injuries; chondrocytes for arthritis; cardiomyocytes to replace damaged heart tissue; insulin producing pancreatic cells for diabetes; cancer treatments; the regeneration of vital organs for transplant patients; and many more uses still to be discovered.

The first case study relating to human embryonic stem cell is about, Molly Nash was a six-year old girl with Fanconi anemia, suffering with a rare genetic disorder, which prevents the production of bone marrow by the body and can kill at a very young age. 2 The doctors suggested that a bone marrow transplant from a matching sibling could offer an eighty-five percent rate of success for treating this disease.3 The parents opted for assisted reproduction and genetic screening with the help of Reproductive Genetics Institute, Chicago for reproducing Molly Nash's sibling. The girl received a transfusion of stem cells from her brother's umbilical cord and placenta. This therapeutic intervention was the first recorded experiment that merged the technologies of genomics and stem cell research.

The luring technology at its raw stage, had to stand the test of the society upon the moral, ethical and social standards. Though legal questions concerning novelty, non-obviousness and industrial applicability raised through patents is answered, the scientists also were made subject to the questions relating to the social acceptability of the technology. The ethical question concerns the status of the human embryos that were created in order to select an appropriate match for treating Molly, especially with regard to treating them as persons having rights or property for medical research. Human embryonic stem cells are harvested from the inner cell mass of a blastocyst-stage embryo and its retrieval is only through destruction of the same. This embryo destruction resulted into the rejection of patent for Edinburgh4, Wisconsin Alumini Research Foundation5 and the CIT6.

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1 Thomson,J. et al. (1998), 'Embryonic Stem Cell Lines Derived from Human Blastocysts', 282 (5391) Science 1145-7.

2 Associated Press (2000), 'Siblings Transplant Seen as Milestone in Embryo Research', Oct 19, Chicago Tribune, 3

3 Denise Grady (2000), 'Son Conceived to Provide Blood Cells for Daughter', Oct 4, New York Times, A24

4 (Edinburgh), T1079/03

The commercial value of the embryonic stem cell increasing day by day and increasing international attention towards the somatic cell nuclear transfer (SCNT) or 'therapeutic cloning'7 is yielding towards 'gold rush'. The main controversy of the latest century relating to embryonic stem cells is with respect to chimeras, trans-species organisms created by mixing stem cells or embryos of different species with early embryos of other species.

The present article is based upon the hypothesis that every technology, though qualifies patentability criteria is also required to oblige the implied limitations which flow from social, moral and ethical standards of the society, the place that technology has to operate. The present article is focused on the cross-jurisdictional study of patentability of the embryonic stem cell and therapeutic cloning. The objective of the article is to see whether in America and Europe, the social, moral and ethical obligations act as limitations upon the embryonic stem cell research and therapeutic cloning or not, and if so, to what is the extent of operation of such limitations?

2. Embryonic Stem Cell Research and Therapeutic Cloning: Generally speaking

Stem cells are defined as cells that are capable of differentiating to give one or more types of mature bodily cells and of dividing to give further stem cells without loss of differentiation potential.8 Based on the cell type/tissue of origin, stem cells are classified into Somatic Stem Cells (SSCs), and Embryonic Stem Cells (ESCs). SSCs have limited differentiation capacity and may be multipotent or unipotent. ESCs on the other hand are pluripotent and this characteristic can also be generated by reprogramming of somatic cells, giving rise to induced Pluripotent Stem Cells (iPSCs). The regulatory requirements for research on stem cells depend on their origin and potency. Embryonic Stem Cells (ESCs) are derived from pre-implantation embryos. Those derived from embryos before differentiation of trophoectoderm and inner cell mass (i.e. morula stage) are truly totipotent, capable of giving rise to the entire organism and extraembryonic tissues. However, ESCs derived from the inner cell mass (ICM) are pluripotent (not totipotent), having ability to differentiate into derivatives of all three germ layers, viz., ectoderm, mesoderm and endoderm, but not placenta.9

Therapeutic cloning involves the replication of human embryos to harvest stem cells for medical uses. Most clones are created through a process called 'somatic cell nuclear transfer'. In this process, from the nucleus of a donor cell, DNA material is pulled out and transferred into a hollow egg. The acquired egg will be destroyed to extract the stem cells, which are pluripotent in nature i.e., having the potential to form any cell or tissue of the human body. These are also called master cells, capable of morphing into cells in the brain, muscles or other organs, and which might be used for medical treatment.

3. Moral, Ethical and Social issues as implied limitations on Embryonic Stem Cell Research and Therapeutic Cloning

According to the standards of patents, any invention fulfilling the criteria of novelty, non-obviousness and industrial applicability are qualified for grant of patent. Patent laws only recognizes the ownership and the related rights, their enforcement etc., The regulations over the application of technology in the society is regulated in the form of exclusions. However, the embryonic stem cell research and therapeutic cloning by developing artificial embryos overcame the patentability requirements. The real question, which the new technology has to face, is the social, moral and ethical objections to such inventions.

Whether social, ethical and moral issues act as implied limitations upon an invention, which qualifies all three requirements i.e., novelty, non-obviousness and industrial applicability laid down by

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5 (Wisconsin Alumini Research Foundation), T1374/04

6 (CIT), T522/04

7 Therapeutic cloning is a process of creating an embryo through a cloning procedure so as to derive human embryonic stem cells for purposes of research and potentially for tissue transplantation. See Mathew Rimmer, 230, n.8

8 Pandey Aparna (2016), Stem Cell Research in India: Socio-Ethical Concerns, 4 (1) International Journal of Advanced Research 282- 289.

9 National Guidelines for Stem Cell Research, Indian Council of Medical Research, Department of Health Research & Department of Biotechnology, 2013, available at http://dbtindia.nic.in/wp-content/uploads/2014/05/national-guidelines-of-stem-cell-research.pdf

the patent legislations? In Kesavananda Bharati v. State of Kerala, Justice Khanna while referring to the concept of implied limitations in the context of Doctrine of basic structure observed that, the concept of implied limitation has two facets, firstly, they are limitations which flow by necessary implications from express provisions of the Constitution, and secondly, limitations which must be read in the Constitution irrespective of the fact whether they flow from express provisions or not because they are stated to be based upon certain higher values which are very dear to the human heart and are generally considered essential traits of civilized existence, which constitute the spirit….. of the Constitution.10. It can be observed from the various judicial precedents relating to the embryonic stem cell research and therapeutic cloning delivered in different countries that the courts accepted moral, social and ethical considerations as an implied limitation.

Position in United States

In United States, the ethics and policy debate on embryonic stem cell research has been initiated after a Congressional ban in 1996 on embryonic stem cell research, restricting the destruction of embryos, discarded, or knowingly subjected to risk or injury. But in late 1998, the University of Wisconsin-Madison research team led by Professor James Thomson and scientists at John Hopkins University led by John Gearhart in collaboration with Geron Corporation, California announced successful experiments in isolating and culturing embryonic human stem cells using somatic cell nuclear transfer. Ian Wilmut, Edinburgh, Scotland in 1997, replicated this process in the cloning of Dolly and later a team of US researchers announced their success in culturing bone marrow adult human stem cells.

In response to the large demand of the public towards embryonic stem cells research, US Government presented two important reports, one by the National Bioethics Advisory Commission (NBAC) and one by the National Institutes of Health (NIH). The NBAC presented a lengthy report titled 'Ethical Issues in Human Stem Cell Research, 1999' and published its revised 'guidelines on embryonic stem cell research, 2000'. According to the NIH guidelines, the use of federally funded research to derive human pluripotent stem cells from fetal tissue, originating from non-federally funded agencies is permitted, provided there was informed consent of the donors and no financial inducements11. In 2001, President Bush approved federal funding for more than sixty genetically diverse stem cell lines and subsequently, the NIH established a web-based human embryonic stem cell registry to accept applications for federal grants and also released a list of stem cell colonies approved for federally funded research.

According to the history in 1979, the US Ethics Advisory Board indicated that it was ethical to create research embryos in order to investigate safety issues for in vitro fertilization technology. It seems likely that it will be this debate on the early embryo that will provide the crucial terrain for regulatory policies on embryonic stem cell research, including the perspectives of religious ethics.12 On November 25, 2001, Advanced Cell Technology in Worcester, Massachusetts, announced that it had successfully cloned human embryos and it has been approved by the stem cell research and therapeutic cloning and ethics committee mentioning that human organism produced by therapeutic cloning is not equivalent to any ordinary human embryo because it did not result from normal egg/ sperm fertilization process.

Till 2012, the USPTO has issued over 8000 stem cells patents, hundreds of patents claiming methods of isolating stem cells, methods of differentiating stem cell lines, and methods of using stem cells in treatment.13 The most dominating human embryonic stem cell patents in US are owned by, WARF 14, Geron 15 and North Carolina State University 16. The WARF patents includes five unmodified stem cell lines, method of isolating human embryonic stem cells etc., In 2006, US based Foundations named, Taxpayer and Consumer Rights and Public Patent Foundation filed before

10 AIR 1973 SC 1461; (1973) 4 SCC 225, 1973 Supp SCR 1.

11 The NIH guidelines sought to establish a distance between the derivation of embryonic stem cells, and federally funded research on these stem cells.

12 Richard M. Doerflinger, (1999), 'The Ethics of Funding Embryonic Stem Cell Research: A Catholic Viewpoint', 9 Kennedy Institute of Ethics Journal, 137- 140.

13 Mathew Rimmer, 237, n.8

14 Patent No.6,280,718.

15 Patent No.7,297,539

16 Patent No.5,340,740

USPTO for re-examination of the claims of WARF patents. The claimed that the WARF patents are based on prior art patent granted to Robert Lindsay Williams. The USPTO upheld all the three WARF patents by attracting huge criticism. Upon appeal, in Foundation for Taxpayer and Consumer Rights v. Patent of Wisconsin Alumni Research Foundation 17 the USPTO Board of Appeals and Interferences rejected the controversial WARF '913 patent claiming pluripotent human embryonic stem cells on the grounds of anticipation based on prior art patent and obviousness.

Position in Europe

Unlike the patent law of the United States, EPC explicitly excludes certain specific types of invention from patentability as matters of principle or public policy even though they qualify the conditions novelty, inventiveness, and sufficiency. The refusal of patents on inventions "the publication or exploitation of which is contrary to ordre public or morality", found in EPC Art.53(a), has a long history of attempted use by the Greens, animal rights campaigners, and others in formal opposition proceedings against specific patents granted by the EPO.

The Directive on the Legal Protection of Biotechnological Inventions18 was legislated in 1998. The Commission's rationale for the Directive was to improve the competitiveness of the European biotechnology industry by clarifying and harmonizing European patent laws. The most notable feature of the Directive is the 'morality clause' in the form of Article 6, which provides a non-exhaustive list of specific examples to be excluded from patentability on the grounds of ordre public or morality. Art.6(2) provides a non-exhaustive list of unethical inventions that would be excluded from patentability which includes processes for cloning human beings, processes for modifying the germ line genetic identity of human beings; uses of human embryos for industrial and commercial purposes;…..". 19

The European Patent Convention, 1973 embodies certain rules regarding the patenting of biotechnological inventions. These rules have been imbibed from the Directive on the legal Protection of Biotechnological Inventions via an amendment. Rules 23b to 23e talk about biotechnological inventions. "Biotechnological inventions" are defined as "inventions, which concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used". "Biological material" means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system.20

Rule 23(c) of the EPC provides for the scope of the patentability of biotechnological inventions. Clause (a) of the Rule says that the biotechnological invention shall be patentable if they concern "biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature;" However, rule 23(d) completely bans the patentability of a procedure that makes use of human embryo for industrial or commercial purposes. At the same time, rule 23(e) of the EPC says that simple discovery of a fragment of formation of any part of the human body including its genetic material will not constitute an invention however an element isolated from the body or produced by technical process may constitute a patentable invention even if it resembles a fragment of the formation of a body part. However, the rule mandates that the industrial application of the body part must be disclosed in the patent application.

In the Onco-mouse case (T19/90)21 case, the decision to grant patent covering the use of laboratory animals genetically engineered to possess increased sensitivity to carcinogens was objected by certain special interest groups. Here, the Technical Appeal Board, instructed the EPO to consider the applicability of Art.53(a) and suggested that the decision, "would seem to depend mainly

17 Foundation for Taxpayer and Consumer Rights v. Patent of Wisconsin Alumni Research Foundation, BPAI No.2010-001854 (28 April 2010)

18 Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213 of 30.07.98, p.12

19 Art.6(2)(c) of Directive 98/44/EC, Section 2(1)(3) of the Austrian Patents Act excludes patents on the use of human embryos per se and not only on the use of embryos for industrial of commercial purposes. Similarly, Article 5 of the Dutch Patents Act excludes patents on the use of human embryos per se, and not for just industrial and commercial purposes. On the other hand the Estonia Patents Act excludes such inventions only if it is for commercial use.

20 Rule 23(b) Clause (3) of the European Patent Convention, 1973

21 Harvard/Onco-mouse, T19/90, 1990, O.J. EPO 12/1990, 476, and 1992 O.J. EPO 110/1992, 588.

on a careful weighing up of the suffering of animals and possible risks to the environment on the one hand and the invention's usefulness to mankind on the other". The EPO decided that the benefit to cancer research outweighed the other factors and sustained the patent. Appeals were filed and the opposition was not concluded until April 2006 by which time the Technical Appeal Board were able to take into account specific provisions in Biotechnology Directive 98/44 (discussed hereinafter) concerning transgenic animals and to hold that the benefit to mankind outweighed the morality objections.

The 'Edinburgh' patent22 was concerned with methods of isolating, enriching and selectively propagating animal stem cells and was granted with claims to the general method of selecting cells, to cell mixtures, including stem cells, transfected with the marker gene and to a method of making a transgenic animal by introducing the transfected cells into a blastocyst. The Division's decision was that human embryonic stem cells per se are not patentable under Rule 23d(c).

The Directive 98/44, established European Group on Ethics in Science and New Technologies as the advisory group to assist on such issues. In November 2000, EGE reported on ethical aspects of human stem cell research and concluded that research should first proceed with the use of spare embryos, fetal tissues, and adult stem cells, rather than by creating embryos for this purpose23. The Group concluded that "isolated stem cells which have not been modified do not, as a product, fulfil the legal requirements, especially with regard to industrial applications, to be seen as patentable", and, further, that "only stem cell lines which have been modified by in vitro treatments or genetically modified so that they have acquired characteristics for specific industrial application fulfil the legal requirements for patentability".

In the continuing case of Oncomouse II (T0315/03),24 the Technical Board of Appeal had found it necessary to analyze the function of r.23d in relation to Art.53(a) and they concluded that the morality provisions by which they are now bound encompass two distinct tests: first, and where apposite, a test based on the wording of the relevant individual subsection of the rule and secondly, a so-called "real" Art.53(a) test which must be applied if the invention under scrutiny survives the first test. In other words, the individual subsections of the rule lie within and do not exhaust the overarching scope of an Art.53(a) objection.

In CIT Patent Application25 claimed a population of mammalian neural crest cells from other embryo cells and uses thereof by Caltech. The EPO refused the grant of patent on the grounds of Article 53(a) and Rule 28(c). The Briistle's patent26, involved the method of converting embryonic stem cells into nerve cells that could potentially be used to treat neurological trauma and disease, with claims directed to neural precursor cells derived from embryonic stem cells and methods for producing the neural precursor cells.27 The Court of Justice of the European Union (CJEU) by expanding the meaning of the 'human embryo' held that it does not only include fertilized human ovum but also non-fertilized human ovum whose division and further development has been stimulated by parthenogenesis. Basing on the above interpretation, CJEU held that a claim directed to 'a cell culture comprising primate embryonic stem cells' is not eligible for grant of patent under the Biotechnology Directive 98/44. The decision clarifies that CJEU interpreted 'human embryo' basing on the capability of 'commencing the process of development of human being'.28

In International Stem Cell Corporation (ISCC) v. Comptroller General of Patents29, the patent was applied relating to methods where parthenogenesis is used to activate a human oocyte. UK

22 European Patent No: 065 351
23 Commision of the European Communities (2003), 'Commission Staff Working Paper Report on Human Embryonic Stem Cell Research, 441, https://ec.europa.eu/research/press/2003/pdf/sec2003-441report_en.pdf
24 Oncomouse II, Technical Board of Appeal (3.3.8) Decision T315/03. Abridged version in OJ EPO 1/2006, 15-82
25 (CIT), European patent no. EP0658194, n.24
26 Patent No.EP1040185, Greenpeace v. Oliver Briistle, Decision of the German Bundespatentgericht (BPatG) of 5 Dec 2006, 3 Ni 42/04.
27 Mathew Rimmer, 241, n.8
28 Sonya Davey, Neil Davey, Qian Gu, Na Xu, Rajet Vatsa, Samir Devalaraja, Paul Harris, Sreenivas Gannavaram, Raj Dave and Ananda Chakrabarty (2015), 'Interfacing of Science, Medicine and Law: The Stem Cell Patent Controversy in the United States and the European Union', 71 (3) Frontiers in Cell and Developmental Biology, journal.frontiersin.org/article/10.3389/fcell.2015.00071/pdf
29 CJEU, 18 December 2014, Case C-364/13

Patent office concluded that parthenogenetically derived structure (parthenote)30 was analogous to the blastocyst stage of normal embryonic development, thus falls under the definition of 'human embryo' and excluded from patenting. According to ISCC, the parthenote is not capable of producing an embryo because it contains only the maternal nuclear chromosome but no paternal DNA. CJEU held that unfertilized human ovum whose division and further development had been stimulated by parthenogenesis does not constitute a 'human embryo'.

Position in India

In India, Reliance Life Sciences, Mumbai is the pioneer in embryonic stem cell research and is involved in developing cell therapies to address neural, cardiac and metabolic disorders. Recognized by the National Institutes of Health, USA, Reliance Life Sciences fully complies with the criteria for derivation of human embryonic stem cells of NIH (USA) and ICMR (India). Reliance Life Sciences has established South Asia's first, most advanced and completely automated stem cell enriched umbilical cord blood repository. The repository holds over 3500 units. This is the first cord blood repository in the world to be accorded a licence by an official regulatory authority, Food and Drug Administration (FDA), Government of India. The Govt. of India to the Indian Council of Medical Research (ICMR), New Delhi, has delegated the task of regulating of stem cell research. ICMR issued National Guidelines for Stem Cell Research in 2013. The guidelines have been laid down to ensure that research with human stem cells is conducted in a responsible and ethical manner and complies with all regulatory requirements pertaining to biomedical research in general and stem cell research in particular.31 First of all, ICMR has, according to the source of stem cells and nature of experiments, categorized the research on human stem cells into following three areas: Permissible research areas32, Restricted research areas33, Prohibited research areas.

Under the head prohibited research areas, research related to human germ line gene therapy and reproductive cloning; In vitro culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier; clinical trials involving transfer of xenogeneic cells into a human host; any clinical research on Zenogeneic-Human hybrids; research involving implantation of human embryos (generated by any means) into uterus after in vitro manipulation, at any stage of development, in humans or primates; breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to gonadal cells have been listed.

The Indian government has set up an Institutional Committee for Stem Cell Research and Therapy (IC-SCRT) and the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)34 to regulate the stem cell research sector. The Government of India following the line of Obama Government in United States of America allocated more than Rs.300 crore towards basic and applied research in stem cell technology. In India, the stem cell research is basically focusing on areas such as regeneration of damaged muscles due to heart attack, stroke or cornea damage35.

4. Conclusion

The introduction of artificial eggs, which are famously known as 'Farms Eggs' in the Indian society in the place of 'Country Eggs' has, became a debate in the olden days. Now, the introduction of concept of artificial embryos in the place natural embryos, though for the purpose of therapeutic cloning also became a talk. The difference in the above two examples is in the 'farm egg' concept, there is no possibility of a chick coming out of such eggs, but where as in the case of artificial embryos, the possibility of its development of a baby out of it, provided it is introduced into the uterus is high. Though United States of America is confronting the questions relating to the social, moral and ethical values of the embryonic stem cell research and therapeutic cloning through the patent standards, the U.S.Congress, the ethical guidelines have been made stringent.

30 A parthenote is an unfertilized egg chemically induced through a process called parthenogenesis to begin developing as if it had been fertilized, and behaves like an embryo in early development.
31 Article 2.0, National Guidelines for Stem Cell Research in 2013
32 In vitro studies on pluripotent stem cell lines viz. ES or iPS cells, or SSCs from foetal or adult tissues, for understanding their basic biology, may be carried out with prior approval of IC-SCR.
33 Creation of a human zygote by IVF, SCNT or any other method with the specific aim of deriving ES cell line for any purpose.

35 http://forbesindia.com/article/briefing/stem-cell-research-advantage-india/9892/1

In case of Europe, the Great Britain is the first country in the world to legalize the creation of human embryos in the year 2001. The purpose of such creation is not for therapeutic cloning but only for experimental usage. The present regulations in Europe allow the creation of artificial embryos with the condition that these clones must be destroyed after fourteen days of their creation. Creating live babies by cloning is prohibited in Europe. India, the Department of Biotechnology, Ministry of Science and Technology issued National Guidelines for Stem Cell Research, 2013. These guidelines, in line with European Directive, states that In vitro culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier. At the end, with the given analysis, it can be concluded that social, ethical and moral issues act as an implicit limitation upon the embryonic stem cell research and therapeutic cloning apart from patent law.
