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Rethink the patentability of human embryonic stem cell research findings: Relaxation based on benefit weighing

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Attitudes toward the patentability of the human embryonic stem cell (hESC) research findings are undergoing dynamic adjustment based on benefit weighing. In the early stage, ethical concerns prevailed: both the United States and China placed restrictions to some extent. As the science and technologies advance, the original balance has been broken. With a series of precedents and policies, the United States relaxes the conditions on hESCs. In this regard, China has established several rules mainly through patent examination practices. These rules are finally reflected in China's revised *Guidelines for Patent Examination* in 2020, which clearly defines the shift in China's stance.

Introduction

The human embryonic stem cells (hESCs) in the inner cell mass of the blastocyst are multifunctional and self-renewing. In ideal conditions, they differentiate into all types of cells on three germ layers, including germ cells, and then develop into any human tissue (excluding the placenta). Theoretically, the hESCs have the totipotency of induced differentiation both *in vitro* and *in vivo*, which brings about the possibility of addressing diseases that cannot be cured with traditional techniques and to repair the damaged and aged organs. In practices, there are many cases on the application of the hESCs. In 2008, a patient with Parkinson's disease in China was cured after stem cells were implanted into the body of the patient for new cell differentiation (Tian et al., 2008). In 2014, Masayo Takahashi, the ophthalmologist at the RIKEN Center for Developmental Biology, transplanted the epithelial cells on the retina in the hESCs onto the retina of patients when treating the age-related retina degeneration diseases, bringing about significant improvement to the vision of 18 patients (Liu, 2014). However, hESC research has long been controversial. According to the Japanese scholar Iwasaki Chikatsugu, the highest goodness is the dignity of human beings and their survival. When human embryos are viewed as research tools, instrumentalization and commercialization risks grow (Chikatsugu, 1993). Modern embryological studies have shown that the embryonic primordial chordate striations appear after 14 days of development, and then begin to differentiate into various tissues and organs, which means that the embryo at this time has the ability to develop into a unique human individual. The Australian philosopher Norman Ford therefore claims that human beings in the real sense do not exist until the 14th after the germ cell forms (Ford, 1998).

In light of the inherent conflicts between the extensive application prospects of hESCs and the possible ethical harms, the patentability of hESC findings is adjusted dynamically based on constant benefit weighing. On one hand, research in this regard substantially promotes scientific progress. Many countries are putting in place protection mechanisms to boost innovation. Patent protection, as the most powerful model, has long been recognized. On the other hand, out of the concerns for ethics and possible monopoly resulting from patent protection, countries placed policy and legislative restrictions on hESC research and the patentability of findings in the past. However, the values of hESCs are further tapped as the research deepens. The patentability is reexamined and established. With the stance shift on the hESCs in China and the United States as the object, this paper aims to reveal the trend.

Divergent stances on hESCs: Ethical restrictions at the early stage

Fund restrictions in the United States

Attention to human embryos. The United States was cautious with hESC research at the early stage, particularly with the fund for related projects. In the *Roe v. Wade* case of 1973, the legality of a women's right to abortion was emphasized again (Roe, 1973). As a result, the legitimacy of fetal research has also been widely concerned by the community. In 1973, the former Department of Health, Education and Welfare (DHEW) (now the Department of Health and Human Services) suspended all projects on human fetus it sponsored or funded. In 1974, Congress passed the *National Research Act,* established the National Committee for the Protection of Human Subjects of Biomedical and Behavioral Research (Committee) to assess research on the fetus, and issued a 4-month ban. Later, DHEW founded the Ethical Advisory Board (EAB), responsible for formulating the standards and proposals for federally funded research on the human fetus and evaluating the special fund applications. However, no proposals had been approved. In essence, before the inauguration of President Clinton in 1993, DHEW had sponsored no research related to human embryos at all (Zhao, 2010).

Establishment of the restriction framework. President Clinton supported human embryo studies and proposed to fund

embryo studies the second day following his inauguration. Congress passed the *Rejuvenation Act of National Institutes of Health* and set up the Human Embryo Research Panel (Panel) to replace EAB. Upon the recommendation of the Panel, Clinton signed an administrative order, allowing the federal government to fund embryo studies in specific conditions, but it was intervened by Congress. Out of the awe for the embryonic ethics, the Congress, as suggested by Representative Jay Dicky from Arkansas (*Dicky Amendment*), revised the annual budget of DHEW in 1996, preventing the federal government from funding any research project that created, destroyed, discarded, or damaged embryos (Fujikawa, 2005). Since then, the government began to adopt a cautious attitude toward the embryonic studies. However, with the successful isolation of hESCs in 1998, research on the corresponding stem cells no longer falls within the scope regulated by the *Dicky Amendment*. It was controversial as for whether such studies can be granted with federal funds. In 2001 when George W. Bush came into power, the Bioethics Advisory Committee was established to evaluate the ethical implications of a series of studies. The Committee concluded that, in spirit of the Dicky Amendment, the embryo should be endowed with the same rights as the fetus, and suggested that the federal government not encourage any research that might damage the embryos. Later, the president signed the administrative order, stating that federal funds can be used to sponsor the ESC lines created before August 9, 2001, only. This move won support from religious groups and social organizations, but many researchers were dissatisfied. With endless efforts, Congress managed to pass the *Stem Cell Research Advancement Act 2005,* which allowed the federal government to fund the newly created ESC lines and was approved by both Houses. But this *Act* was vetoed by the president. In 2007, the *Act* was passed by the Congress and vetoed by the president again.

Analysis and evaluation. The early restriction framework in the United States was basically shaped during the Bush administration, and the corresponding time started from the Roy case in 1973 to the second veto by George W. Bush in 2007. Although the federal government has neither ordered nor restricted the development of embryo research supported by private funds, it has always held a negative attitude on whether such research should be funded by federal funds, which was of profound impact. On one hand, many top American scientists conduct scientific research at colleges and universities, and much of the funds came from the government. The restrictions on the research areas cut off the source of funds, resulting in severe talent loss and slowing down related research. On the other hand, biotech is a risky area for investment activities. The governmental attitude has enormous impact on investors. The fund restrictions dampened the investment enthusiasm and adversely influenced the costly research in this area. Most importantly, as stipulated by the government, only the hESC lines created before August 9, 2000, could be funded. This reduced the sample size and the research scope, limiting the possibility of further development. According to the statistics released by National Institutes of Health (NIH), approximately 60 hESC lines were created before August 9, 2000, across the world (Fowle, 2004). Due to the loss of characteristics and gene mutation of stem cells *in vitro*, the number of cell lines available for use will gradually decrease, which is undoubtedly a reverse development in the United States

Ethical restrictions in China

Policy guidance and control. In terms of the origin of human beings, there are certain differences (mainly religious) between China and the West. But it does not mean that China does not accept the ethics about embryos. According to the gradualism of Confucianism, the life of a human begins with birth rather than the formation of the germ cell. Therefore, a human embryo is not a human (Qiu and Zhai, 2009). Good customs is the basic principle of China's civil law and the reflection of ethics in laws. China's ethical concern stems from human cloning and the damage of human genetic consistency (Lei and Qiu, 2019). Therefore, the ethical restrictions on human embryos in China adversely impacts the legislation and practices, while China's policies play a facilitating role. In October 1998, the Chinese National Human Genome Center at Shanghai was founded, and the *Codes of Ethics on Human Embryonic Stem Cell Studies (Draft)* was released in 2001. Although related findings could not be protected as patents, some research was allowed to conduct by the law, creating room for the development of the stem cell technologies in China. In the following years, related guidelines were released, five of which were made public in 2003 only. The former Ministry of Health (National Health Commission of PRC now, CNHC) released the *Guidelines on Assisted Human Reproductive Technology*, the *Codes of Ethics on Assisted Human Reproductive Technology Implementation* and the *Ethical Review Procedures of Biomedical Research Involving Human Beings*, stipulating the underlying rules and scope of hESC research, the access to obtain the hESCs, and the inspection supervision measures. The National Medical Products Administration of PRC (CNMPA) issued the *Guidelines on Human Gene Therapy Research and Preparation Quality Control Technologies* and the *Guidelines on Human Cell Therapy Research and Preparation Quality Control Technologies*, regulating clinical gene editing research on hESCs. The hESC research in China was thus standardized by these polices.

Strict restrictions on clinical application. Along with the progress in fundamental research, conditions for clinical trial and application became mature; however, China placed

strict policy restrictions. The restrictions were closely related to the ethical considerations. As human embryo research is further developed, some organizations, attracted by the enormous profits, began to engage in stem cell application, treatment, and cosmetic surgeries secretly. Some of these activities were not covered by the regulations and there was a growing ethical concern among the public (Liu, 2018). In response, CNHC released the *Regulations on Clinical Application of Medical Technologies*, transferring the supervision responsibilities from the provincial health institutions to CNHC, elevating the review standards and the threshold for clinical application, and highlighting the ethical examination. Later in 2011, the *Notice on Self-Examination and Correction of the Clinical Research and Application of Stem Cells (Notice)* stopped the stem cell research and application activities that were not approved by CNHC and CNMPA, and do not accept any application projects before July 1, 2012. In 2015, CNHFPA and CNMPA co-formulated the *Regulations on the Clinical Research of Stem Cells (Trial)*, specifying the institutional conditions and duties on hESC organizations, application and registration procedures, research processes, reporting system and supervision, and so forth. The hESC research was further standardized and the Ethical Board was to be established.

Evaluation and analysis. The ethical influence of hESCs is a gradual increase in China. The restriction framework was established in 1998 when CHGC (Chinese National Human Genome Center) was founded and took on the basic form in 2011 when the *Notice* was released. Based on different understandings of the origin of people, the development of corresponding research in early China was not strongly restricted by religion, and public order and good customs became the concrete embodiment of ethics and morality in related research. However, under the attraction of huge economic interests, there are many nonstandard abuse phenomena in China's industry. Due to concerns about ethical risks, the corresponding clinical application is forced to slow down, and China has issued a number of policy documents, from raising the access threshold to stopping illegal operations, and even resulted in a "vacuum period" in the approval of human embryo research (Zhao and Wu, 2015). After that, more regulations were developed to specify the general policies and step up supervision. Behind a series of measures, ethical considerations are implied, which makes the development of clinical application in China lag behind other countries in this period.

Re-adjustment based on the value of hESCs

Stance shift of the United States

Removing fund restrictions. The restriction policies issued by George W. Bush slowed down hESC research in the United States, impeding scientific progress and possibly causing the United States to lose the leading edge in this area. To improve the conditions, President Obama in his speech on March 9, 2009, made it clear that the medical application of hESCs enjoyed great prospects and he hoped such research would help improve public health. President Obama reiterated the stance of "no political intervention over science." On the same day, the president signed the administrative order to remove the federal fund restrictions, allowing scientists to research the newly created hESC lines worldwide with federal funds. But the *Dicky Amendment* remained effective, leaving the hESC research in gloom. The NIH once published guidelines to implement the administrative order signed by Obama, which eased the restrictions placed by the former president and funded the researchers with many newly created hESC lines (Tang, 2013). This move invited opposition. In August 2009, James Sherley and Theresa Deisher sued Kathleen Sebelius (head of DHEW) and Francis Collins (head of NIH). The local court of Washington, DC, issued a temporary ban to stop the NIH-funded research for 17 days. In the subsequent appeal, the appellate court revoked the ban. Finally, the Supreme Court rejected the request of stopping the hESC research funded by the government. Despite the ethical controversies, the restriction framework was abandoned, and related researches can be funded by the federal government.

Re-affirming the patentability of hESC-related findings. When devising the Patent Law in 1952, the Senate and the House of Representatives both made it clear that the patent projects all things created by human beings under sunshine, specifying the scope of patentability. The patentability of hESC-related findings suffered not much resistance in the United States. For instance, the Wisconsin Alumni Research Foundation (WARF) held a series of fundamental patents, such as Patent No. 806 pointing to hESCs and Patent No. 913 as a continuation of Patent No. 806. Both inventions were patents in the United States. On July 17, 2016, the American Public Patent Foundation (PUBPAT) and the Taxpayer and Consumer Rights Foundation (FTCR) asked the US Patent and Trademark Office (USPTO) to reexamine Patent Nos. 806 and 913 on the grounds that such patents lacked nonobviousness, because they had been proved in the acquisition of mice ESCs. USPTO made a nonfinal rejection to these patents in 2007 on the grounds that they did not meet the nonobviousness requirements. Based on review and debate, USPTO finally believed that the previously existing technologies were too unpredictable to allow other scientists to culture hESCs and accepted the nonobviousness of the WARF patents. USPTO sustained Patent No. 913 in February 2008, and Patent No. 806 in March of the same year. This case shows the American attitude toward the patentability of hESC-related findings.

Easing restrictions in China's trials

Admitting the legitimacy of the commercial sources of hESCs. It is difficult for the hESC-related findings to get patented because they often come from human embryos. The findings have ethical implications and can therefore not be patented. However, the hESCs can survive and proliferate *in vitro* (Thomson et al., 1998). At present, more and more hESC lines were created and a stable commercial chain that supplied hESCs came into being. China refused to authorize these commercial hESCs at the early stage (Yi and Ma, 2012). In 2001, the WARF's application of *the method that prepares the embryoid from the primary hESCs* (No. 22325) *was rejected*. On further investigation, the Patent Reexamination Board of CNIPA (CPRB) sustained the denial on the ground that such hESCs originated from human embryos, although the applicant had made it clear that the cultured hESCs came from the commercial lines. With the technologies available then taken into consideration, the abstraction of the hESCs would inevitably damage the embryos. The source tracing practices did not stop until 2010 when the reexamination resolution of *the method to induce the differentiation of the hESCs into the liver cells and the dedicated culture medium* (No. 24343) was made public. The CPRB broke the precedent and believed that the induced differentiation method was not against the ethics if the implementation of such method did not damage the human embryos, although the hESCs obtained with this method were put into industrial or commercial application. This case is of great significance and has affected many subsequent review decisions, representing the stance changes in the patentability of hESC-related findings (Liu and Jiang, 2018).

Types of hESCs. China's current legislation does not provide a clear definition of hESCs. In the practice of patent examination, not only is it not distinguished, but it is often interpreted as a process of human development, excluding its patentability (Liu and Xu, 2019). When reexamining *the hematopoietic cells derived from hESCs* (No. 27204), the CPRB believed that the undifferentiated hESCs have the totipotency of differentiation and can differentiate into a human being. It can be classified as a human body at various stages of formation and development, so it is also an invention that cannot be granted a patent. This extremely broad identification model was changed in the reexamination resolution of *the nuclear re-programming factors* (No. 26398) in 2015. According to the Board, human cells with no totipotency did not belong to human embryos, and the biological method inventions arising from such cells were therefore not against the ethics. The reexamination also ruled that the commercially obtained stem cells should not be viewed as sourcing from human embryos directly or violating the law. It suggests a neutralizing attitude toward hESC application in China.

Revision and promulgation of China's Guidelines for Patent Examination *2020*

Background and contents. The stance changes toward human embryo research in China are mostly found in the patent examination practice, with a series of adjudication rules being established. However, China adopts the civil law system and the precedents in the examination practices are of reference value only. The rules are therefore not strictly followed. The examination standards are under constant changes, which poses challenges not only to examination but to application. Therefore, it is of urgent need to legislate the examination rules. China's regulations on the patentability of hESC-related findings basically come from the *China Patent Law (CPL)*, the *Patent Law Implementation Guidelines (PLIG)*, and the *Guidelines for Patent Examination (GPE)*. Devised based on the CPL and the PLIG, the GPE details the patent application and plays a crucial role in patent examination practices. The GPE (2020) absorbed the adjudication rules of many patent examination cases: on one hand, it adds the exclusions to the part of "industrial or commercial application of human embryos," making it clear that if the invention and creation use human embryos that have not been developed *in vivo* and are fertilized within 14 days to separate or obtain stem cells, the patent right cannot be refused on the ground of "violating social morality" (GPE 2020 Part 2, Chapter 1, section 3.1.2, section 3: however, if the invention or creation is to separate or obtain stem cells from human embryos within 14 days after fertilization without *in vivo* development, the patent right cannot be refused on the ground of "violating social morality"). This statement affirms the legitimacy of obtaining the hESCs under certain circumstances; on the other, the deletion and modification of the contents in Chapter 10 of Part 2 makes it clear that hESCs do not belong to any stage of human development, allowing the possibility that the hESC findings and their preparation methods get patented (deletion and addition of GPE 2020 in section 9.1.1.1, Chapter 10, Part II Delete: "human embryonic stem cells and their preparation methods belong to inventions which cannot be granted patent rights as stipulated in Article 5, paragraph 1 of the Patent Law." New: human embryonic stem cells do not belong to the human body at all stages of formation and development).

Significance and impact. The hESC findings can hardly get patented in China because several basic concepts are not clear. No interpretation is made to "industrial or commercial application" or to "human embryos." As a result, the concepts are inappropriately expanded in the patent examination cases. A set of strict examination standards thus come into being. This revision does not specify the contents of "industrial or commercial application," but confirms the legitimacy to obtain hESCs during specific conditions by adding exclusions. The adjustment signals that the

commercially obtained hESCs conform to good customs, materializing the examination rules and putting an end to the improper tracing of the source of hESCs by the patent examination institution. Also, the GPE changed the attitudes toward hESCs and their preparation methods, stopping the legislation via negation and retaining the extension of related legal regulations so as to better handle the challenges from technological progress. It leaves room for hESC classification and patentability in the new technical mode in the future. In addition, China's policies on hESCs have long deviated from the legal regulations. The *Guidelines on Human Embryo Stem Cell Research Ethics* released by the former Ministry of Health in 2003 have specified the legitimacy of the hESC research that uses the *in vitro* stem cells within 14 days upon the fertilization or nuclear transplantation (hESC research ethics guidelines [2003] Article 6: to conduct human embryonic stem cell research, the following code of conduct must be complied with: blastocysts obtained by *in vitro* fertilization, somatic cell nuclear transfer, parthenogenetic replication technology, or genetic modification, and the *in vitro* culture period shall not exceed 14 days from the beginning of fertilization or nuclear transfer). However, related legislation denied this concept. In response to the policy support, this revision approves the patentability of hESC-related findings and lays solid foundation for the progress of China's biotechnologies.

Summary

By reviewing the evolution of the patentability of hESC-related findings in the United States and China, it can be found that the stance toward the patentability is under constant adjustment. There is a strict-to-easing trend in both countries. In this positive position, the transformation of hESCs has ushered in a new climax. In the research and development of stem cell drugs, since the European Union approved the first listed stem cell therapeutic drugs in 2009, the United States, Australia, South Korea, and Canada have successively launched stem cell drugs. By the end of 2020, the world had approved 25 kinds of stem cell therapeutic drugs, Among them, the United States has the largest number of approvals of 12, nearly half, followed by the European Union and South Korea, with four each. In addition to the products already on the market, many stem cell treatment products have entered phase II/III clinical trials, and it is expected that there will be a number of stem cell products for the treatment of difficult diseases on the market in the next 5 to 10 years. In this regard, although China has not approved any stem cell drugs, as of September 2019, a total of 118 institutions have completed the filing of stem cell research institutions, and 62 stem cell clinical research projects have completed the filing, which has great potential. Hence, it can be predicted that under the change of position from strict to easing, hESC research will usher in a new spring.

Declarations

Data and code availability. The Chinese patent application information (please refer to the label in the article for the specific application number) involved in the article can be searched in the "Patent Search" section of the official website of the State Intellectual Property Office of China at: http://www.cnipa.gov.cn/, last visit date July 21, 2020.

The full text of the patent reexamination resolution involved can be checked in the "Decision Inquiry" of the Patent Office Reexamination and Invalidation Department of the State Intellectual Property Office of China (please refer to the label in the article for the specific application number), website: http://reexam.cnipa.gov.cn/, last visit date July 21, 2020.

AUTHOR CONTRIBUTIONS

Jiajv Chen organized literature and wrote articles. Wei Li wrote the article, and made substantial revisions and improvements. Both authors have made substantial contributions.

CONFLICTS OF INTERESTS

The authors declare no competing interests.

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