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Influence of Patents on Embryonic Stem Cells Research

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This article mainly examines stem cells related patents. We first provided a general background on patents. Then, we investigated patents and how they influence innovation in general, and stem cells in particular. Challenges to patenting inventions and innovations associated with stem cells' field of study in the US and Europe are provided.

Keywords: Patent system; microeconomic; macroeconomic; new drugs; stem cells; influence innovation.

1. INTRODUCTION

A patent is an exclusive right granted by governments or states to an inventor or his/her assignee for a time period in exchange for disclosure of an invention to the public [1]. A patent is not a right to use or apply the invention. Rather, a patent provides the right to prohibit others from using, making, importing, selling, or offering for sale the patented invention for the term of the patent [2]. The patent term typically is 20 years from the filing date, subject to maintenance fees payment. Thus, a patent can be considered a limited property right offered by governments to inventors in exchange for their agreement to share the inventions details with the public [2]. Like other property rights, a patent can be licensed, sold, transferred, given away, or abandoned.

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Table 1. Comparison between what patents can do, and what they can't do [5-7]

What patents do	What patents don't do
Grants the holder the right to prevent others from using, making, selling, or offering for sale an invention without his consent for a limited period. This period differs according to type of invention or country. In many cases, it is about 20 years from filing.	The grant of a patent does not authorize its holder to use or implement an invention, but merely entitles him to exclude others from using it.
Provides a strong incentive to innovate and invest with a view to bringing a product to market.	Patents are not a suitable tool for preventing abuse or risks associated with a given technology.
Advances science and technology by allowing others to build upon the work of others.	Patent law does not replace national, or international law which may impose restrictions or prohibitions on a certain use of technology.

Abraham Lincoln said that patents "add the fuel of interest to the fire of genius" [3]. When they were first introduced, patents weren't created out of a sense of natural justice but rather to encourage and spur innovation. According to international agreements and national laws, the requirements placed on the patentee, the process for granting patents, and the extent of the exclusive rights vary greatly between countries. However, a patent application typically must include one or more claims defining the invention. This invention must be non-obvious, new, and industrially applicable or useful [4]. Certain subject areas remain unpatentable in many countries. For example, mental acts and business methods can't be patented [4].

The rights conveyed by a patent differ between countries. For instance, in the US patents can be applied to all fields of research, with the exception of purely philosophical inquiries. A patent in the US can be infringed as a result of any production or making of the patented invention. A patent also will be infringed by a production or making that goes toward the development of a new invention that itself is possible to be patented [2]. Being an exclusionary right, a patent does not inevitably give the patent owner the right to abuse the patent. For instance, several inventions merely are enhancements of prior inventions that could be covered by a patent for someone else. If an inventor takes an existing patented mousetrap design and adds new features and produces a superior mousetrap, he can get a patent for his improvements and can produce and sell the new product, if he has the permission of the original patent holder, and assuming the original patent remain enforced [5]. The inventor of the improved mouse trap can prohibit the original patent holder from using the improved invention [5].

2. HOW DO PATENTS AFFECT INNOVATION?

The origin of the modern patent system could be linked to the Statute of Monopolies, which was passed in 1624 by the English Parliament [8]. This act's function was to restrain the crown's exploitation, which used the patent system as a royal grant, bestowed to reward and assist friends and supporters, not to reward innovation [8]. The first modern patent law was introduced in the UK in the form of the Patent Law Amendment Act of 1852 [9]. Several economists and historians have argued that there might be a link between the industrial revolution and the introduction of this patent act [8-10]. Research carried out by Varga *et al*. tried to empirically answer the question, "Is it possible to link the industrial revolution to the patent system or are there other factors involved?" They examined this relationship from a quantitative approach, and concluded that patents were not crucial to innovation in the period of interest. They argued further that it is difficult to draw conclusions on this issue [11]. With so many other factors that affect innovation, both macroeconomic and microeconomic, it is uncertain that patents had any impact either negative or positive, other than a minor one. Furthermore, it is difficult to differentiate patents from the culture they were part of. It is expected that a society that awards patents must has advanced to a level of considerable legal and economic sophistication, be conscious of innovation, and possesses a culture of scientific enquiry.

Several studies have been conducted to measure the effect of patents over the advancement of science in modern times [12-14]. For example, Chen used Poisson regressions and negative binomial regressions to empirically measure the relationship between patents and innovation for different countries [14]. Their data showed that after controlling for each country's economy size, there is a significant positive effect of patent laws on invention rates. It remains difficult, however, to establish a cause and effect relationship between adherence to patent laws and advancement of science in general. Nonetheless, from a theoretical point of view, the existence of a patent law presents an additional option value to inventions [14].

On the other hand, patents have the potential to slow down innovation. Competitors in the same field of research could be hindered from conducting research or improving a patented invention even if they possess superior proficiency in the relevant fields. For instance, competitors of Thomas Edison were forced out of business even though they made subsequent technical improvements of their own to Edison's work. This was due largely to the fact that Edison managed to get a broad patent on his improvements to the light bulb [7]. The Wright brothers refused to license their airplane patent at first and finally agreed to license it after World War I [7].

Another obstacle is the monopolistic nature of patents. For example, if a company possesses a patent on a lifesaving pharmaceutical product, this company has the ability to control and set the price for each country for the duration of the patent [15]. Such products sometimes could be expensive for patients who can't afford them, leading to premature death. This has been the center of a dispute between GlaxoSmithKline (UK) and Cipla Ltd. (India) in 2000. GlaxoSmithKline developed and manufactured the life-prolonging human immunodeficiency virus (HIV) drug Combivir®, which is a combination of two antiretroviral drugs, lamivudine and zidovudine. Cipla Ltd. produced a generic version and sold it under the name Duovir® at a cheaper price, disregarding the international patent imposed by GlaxoSmithKline. GlaxoSmithKline claimed that without intellectual-property protection, it would have no incentive to invest the millions necessary to discover and develop new drugs [16]. Cipla Ltd. argued that life saving pharmaceutical products should be available cheaply in the developing world [15]. At present, about two million people die every year from HIV. There are around 33 million HIV patients worldwide, and 70% don't have access to AIDS treatments [17].

3. TRAGEDY OF THE COMMONS AND ANTICOMMONS

About 30 years ago, Garrett Hardin introduced the metaphor "tragedy of the commons" in the academic journal of the *American Association for the Advancement of Science* [18]. The metaphor was introduced in order to clarify the issues of air pollution, overpopulation, and extinction of species. Garrett argued that common resources often are overused by people since there is no reason to conserve. The metaphor nowadays is central to debates in science, economics, and law and is used to justify privatizing common property [19]. While the metaphor underlines the effects of overuse when too many people are allowed by governments to use a limited common resource, it neglects the likelihood of underuse when people have the right to exclude others [19].

Ever since Garrett's article was published, research in biomedical sciences has been moving away from a commons model in the direction of a privatized model [20]. In the US, prior to 1980, the federal government, under the commons model, sponsored upstream or premarket research and allowed the broad distribution of information and research results in the public domain. As a result, unpatented biomedical discoveries were incorporated without restraint in the development of downstream products for the treatment and diagnosis of disease. However, in 1980, in order to promote the development of new technologies, the US Congress started to encourage patenting of discoveries by federally-funded R&D carried out by institutions and universities. In addition, it encouraged the transfer of their technologies to private sectors [20]. As a result, private investments and patent filings increased, leading to applause by supporters. Critics, however, were concerned with the resulting deterioration in upstream research culture [21].

In contrast to Garrett Hardin metaphor "tragedy of the commons," we have the term Tragedy of the Anticommons, which was coined by Michael Heller in 1998 [22]. Anticommons property can be considered the mirror image of commons property. Tragedy of the commons occurs when too many people have a privilege to use a given

resource without being able to exclude others; thus, resources are subjected to overuse. On the other hand, tragedy of the anticommons occurs when a resource is prone to underuse due to the ownership by a small number of people, each with the right to exclude others from using the resource. In theory, commons or anticommons tragedies can be avoided through trading rights [23]. However, avoiding such problems in practice requires overcoming strategic behaviors, transaction costs, and cognitive biases of participants. Success in such endeavors is more probable within close-knit communities than between unreceptive strangers [23].

Biomedical anticommons can be caused inadvertently by governments in two ways: first, by the creation of too many simultaneous intellectual property rights fragments for prospective future products, and second, by allowing too many upstream patent owners to accumulate licenses over future discoveries of downstream users [24]. Patents and other types of intellectual property protection can lead to a more reasonable distribution of profits across all stages of R&D, as well as strengthen incentives to carry out uncertain research projects. However, they also can lead to problems when too many patent or intellectual property owners have rights in prior discoveries that may hinder future research [24]. When they were first introduced, upstream patent rights were intended to assist in attracting private investment. Nowadays, they are more and more considered as entitlements by those who carry out research by means of public funds [25]. Researchers who used to consider themselves entitled to co-authorship now may consider themselves entitled to receive a royalty under a material transfer agreement or to be a co-inventor for a certain patent. This has resulted in a spiral of related patent claims owned by diverse holders [25]. Institutions and their researchers may dislike access limitations imposed over patented discoveries of others. However, no one is willing to offer his or her research findings freely to the public domain.

Regarding stem cell research, there are expectations that the field already may be associated with anticommons [26,27]. This is due to all the patents granted and the overlapping of the claims, which affects the freedom to operate and conduct research. This will lead to growing royalty payments and impose multiple layers of transaction costs. In addition, this can affect the whole field of stem cells, dampen the interest in commercialization, and slow down the advancement of research in the field of stem cells. There are proposals to change the guidelines associated with granting these patents [28, 29]. However there are arguments that it already is too late to change or alter the laws, and that damage already has been done. The best alternative could be a more efficient exchange – redistribution or transaction of granted property rights between scientists and stem cells research centers.

4. EMBRYONIC STEM CELLS PATENTS

4.1 United States of America

James Thomson, a professor at the University of Wisconsin's Regional Primate Research Center, reported in the November 6, 1998 issue of the journal *Science* that he was able to develop the first line of human embryonic stem cells [30]. He claimed that these cells should be useful in transplantation medicine, drug discovery, and human developmental biology [30]. Following the discoveries Thomson's sponsoring nonprofit organization, the Wisconsin Alumni Research Foundation (WARF) applied for three fundamental patents [31-33]. The US Patent and Trademark Office (USPTO) issued the three patents and they apply in the US. WARF also filed with the European Patent Organization (EPO) but not in Asia.

Three patents related to embryonic stem cells were issued for WARF by the USPTO. The first is patent number 5,843,780, issued in December 1998. In this patent, WARF claims the general class of primate embryonic stem cells [31]. The second is patent number 6,200,806, which is very similar to the first patent in regard to claims, but instead of primate embryonic stem cells, this one is concerned only with human embryonic stem cells [32]. The third patent (number 7,029,913) describes the maintained reproduction of human embryonic stem cells without a protein normally expressed in the developing embryo, known as the growth factor leukemia inhibitory factor (LIF) [33]. WARF, in its patents, has broad claims in which it declares the right to the process of making human embryonic stem cell lines as well as the composition of matter or described characteristics. The claim of described characteristics is the main point in their patent application, since it trumps the product of any other process invention that might produce human embryonic stem cell lines. As a consequence, WARF can charge fees or

Table 2. List of WARF's patents and claims at the USPTO [31-33]

US patent number	File/issue date	Composition claims	Claimed cell surface markers	Process claims
5,843,780	18 January 1996/1 December 1998	Pluripotent primate embryonic stem cells	stage-specific embryonic antigen (SSEA)-1 negative, SSEA-3 positive, SSEA-4 positive, express alkaline phosphatase	Method of isolating primate embryonic stem cell line
6,200,806	26 June 1998/13 March 2001	Pluripotent human embryonic stem cells	SSEA-1 negative, SSEA-4 positive, express alkaline phosphatase	Method of isolating human embryonic stem cell line
7,029,913	18 October 2001/18 April 2006	Pluripotent human embryonic stem cells	SSEA-1 negative, SSEA-4 positive, express alkaline phosphatase	No claims

royalties to anyone who wants to produce, sell, or use human embryonic stem cells where the patent is enforced. Several scientists have criticized WARF's strategy and argued that WARF is adopting an unusually restrictive and aggressive policy toward scientific and educational institutions, thus slowing down the ability of researchers to advance this field of research, as well as slowing down the distribution and production of human embryonic stem cell lines [34-36].

WARF's main commercial partnership in regard to human embryonic stem cells is with Geron, which has an exclusive license to develop diagnostic and therapeutic products from human embryonic stem cell-derived cardiac, pancreatic, and neural cells. Thus, according to the issued patents, research can be carried out on human embryonic stem cells. However, any emending commercial application has to be approved first by Geron, in addition to an agreed royalty payment [35].

The New York-based Public Patent Foundation and The Foundation for Taxpayer and Consumer Rights (known now as Consumer Watchdog) have raised concerns about the constrained licensing attitude, broad reach of WARF's patents, and WARF's assertion that it aims to extract fees from the California Institute for Regenerative Medicine related to any income the state might receive from discoveries [37]. The Foundation for Taxpayer and Consumer Rights was involved in Proposition 71, also known as the California Stem Cell Research and Cures Act, passed to support stem cell research in the state of California (in 2004) [38]. The USPTO was asked by the Foundation for Taxpayer and Consumer Rights attorneys to revoke the patents by Thomson on two grounds – first, that the patents considerably overreach, and second, the methods described in their claims are considered prior art since they already were published in the public domain by other researchers [37]. This was supported by several well-known stem cell researchers. They argued that the main reason that researchers competing with Thomson didn't apply their knowledge in a human system is that they didn't have the financial resources required to successfully apply the prior knowledge to a human system [35,36,39].

In March 2007, the USPTO declared all three patents invalid in a preliminary ruling [40]. The USPTO agreed to a degree with the arguments put forward by the Foundation for Taxpayer and Consumer Rights and established that the claims were predicted by prior patents disclosures, and that the disclosed claims by Thomson can be considered obvious to an individual with normal ability in the field of research utilizing accessible public information at the time of the patent application. Several argue the ruling should allow researchers to pursue human embryonic stem cell research more freely in addition to dealing a severe blow to WARF's monopolistic position [41]. However, a reexamination should take place and three matters need to be resolved. First, unsuccessful reexaminations can result in a stronger patent for WARF. Second, for the duration of the appeals and reexamination, the patents remain enforced. Finally, a lengthy appeals process can be carried out by WARF [40].

Patent challenges in the US are common and it is not a sign of inherent weakness in the granted patents. The opportunity for outside experts or the public to challenge or comment on a pending

patent application does not exist under the US patent system. Inventions are assessed only through uncovered information by the examiner or through published disclosed literature by the applicant [25]. There are two means by which to attack a granted US patent, either by using the invention without a license or by starting a business infringing on the patent/ both of these methods usually are associated with lawsuits whereby the challenger ask the court to declare the patent invalid [25]. These strategies have serious disadvantages, since the challenger has to invest in the patented technology without prior knowledge if the challenge will be rejected, and then have to pay the patent holder royalties as well as damages. In addition, lawsuit costs nowadays easily can reach millions of dollars. Another alternative and inexpensive strategy, compared to lawsuits, is patent reexamination through a petition to the USPTO [35]. Reexaminations are comparatively less risky and costly than lawsuits. Furthermore, they can be started before any investment that could infringe the patent is made by the challenger. However, reexaminations have shortcomings as well. For instance, a reexamination does not provide a challenger the right to ask questions of the patent holder or challenge its submissions, and only provides a limited opportunity to present evidence to the USPTO. Furthermore, the final decision in reexaminations is made by the USPTO [35]. On the other hand, invalidation lawsuits include cross-examination of experts as well as liberal policies regarding evidence introduction. Moreover, the jury or judge making the decision regarding the patent is independent of the original patent granting organization, the USPTO [35].

Patents in the field of biotechnology are relatively more susceptible to challenges. However, a long time is required to resolve challenges in this field. It is estimated that the USPTO would require an average of 6.5 years in order to resolve a challenge [42]. The patent holder is favored by such long resolution times, since the patent stays valid and enforceable until a resolution is reached. A famous case that involves long resolution times is the case known as Cabilly II, named after lead inventor Shmuel Cabilly [43]. Cabilly II is an all-encompassing monoclonal antibody manufacturing patent owned by Genentech and due to expire in 2016. Genentech is adamant to protect and appeal any decisions related to the Cabilly II patent since it has earned about US$100 million from it [43]. Entities selling or planning to sell a product made with the monoclonal antibody manufacturing method covered by the patent have to pay license fees or royalties to Genentech. Such products include Remicade® by Johnson & Johnson, Humira® by Abbott, Erbitux® by ImClone, and Synagis® by MedImmune. The patent claims were rejected by the USPTO after a reexamination carried out in 2005 [43]. This was followed promptly by an appeal to the USPTO from Genentech. In 2007, the patent claims were rejected again. However, in February 2009, the USPTO ruled in favor of Genentech and upheld the patent claims. The decision made the Cabilly II patent valid through 2018 and made the patent stronger than before [44].

The Cabilly II patent case should provide insight to the challenge to WARF's patents. One could be inclined to believe that the indecisiveness regarding the challenge could lead licensees to stop paying royalties to WARF or even to unlicensed activities. This, however, was not the case for the Cabilly II patent and it is not expected to occur, since companies that rely on unlicensed use of patented technologies are not likely to be funded by investors while the result of a reexamination is undecided. If a competing group develops a new product utilizing the patented technology, and the challenge presented to the USPTO is not successful, the group could face violation claims as well as demand of future royalties and claims for damages. Geron and WARF remain able during the course of the reexamination to extract fees and royalties from licenses since patents remain in force during reexaminations [42]. Thus, when a licensee declines to pay the licensor and the patent eventually is found legitimate, the licensee might risk losing its right to utilize the patented technology as well as the possibility of having to pay considerable damages [42]. In order to counteract the preliminary USPTO decision, WARF has narrowed and modified its patent claims. It also has incorporated three new claims and distinguished between the prior art of mouse embryonic stem cell culture methods compared to Thomson's method for obtaining primate embryonic stem cells [33].

In 2008, the USPTO patent examiners reversed the revocation order over WARF's patents and upheld the patent claims [36]. However, the Foundation for Taxpayer and Consumer Rights was allowed to appeal to the Board of Appeals and Interference (BPAI) at the USPTO regarding the validity of one of the three patents –

#7,029,913 – and on April 28, 2010, the BPAI of the USPTO overturned an earlier verdict that upheld the claims of that patent [45]. The impact of this decision remains unclear. Researchers and opponents of WARF and the consumer watchdog groups have described the USPTO's decision as a big win for the advancement of the research in the field of human embryonic stem cells [45]. On the other hand, Geron, the biotechnology firm based in California that has the patent license from WARF, believes that the decision by the USPTO is not final and that further examination is due [46]. David Earp, Geron's senior vice president of business development and chief patent counsel, said that "this is not a final rejection of the patent claims. We are confident that WARF will make a strong case in support of the patentability of these claims in continued examination" [46]. John Simpson, the stem cell project director at Consumer Watchdog, has an alternative point of view regarding the USPTO's ruling. He believes that "this is a major victory for unfettered scientific research that could lead to cures for some of the most debilitating diseases" [45]. The latest decision by the USPTO still can be appealed by WARF by asking for a new trial. There also is the option to change the patent claims or provide new evidence and information that was not disclosed previously to the patent examiners at the USPTO. According to Consumer Watchdog, just one of the three patent rulings can be pled by the two opposing parties under current patent law [45]. However, the ruling by the Board of Appeals represents a precedent that ultimately could lead to revocation of the two other patents.

4.2 Challenges in Europe

The response and issues raised in Europe regarding the WARF patents are different from the US. In 1998, in order to harmonize patent laws among member states, the European Union (EU) adopted the Directive on Biotechnological Inventions (Directive 98/44/EC), which deals with biotechnology-related patents, including human genes [47]. Two articles in the directive – Articles 5 and 6 – deal mainly with biotechnology patents. Patenting of the human body at the different stages of its development and formation is prohibited under Article 5. On the other hand, patents on inventions that are contrary to morality or public order are prohibited in Article 6. In addition, inventions that cannot be patented, such as procedures for altering the genetic identity of humans through germlines and the use of human embryos for commercial or industrial purposes, and human cloning are listed in Article 6 [47]. The goal of the directive and articles was to illustrate and clarify the existing agreement in the EU on the kind of inventions that were regarded morally unpatentable during that time. Nonetheless, the division between European courts and national authorities over the implementation of the directives obscured patenting strategies and resulted in substantial legal vagueness in this field [48].

Patents issued by the EPO are governed by the 1973 European Patent Convention (EPC) treaty. A consistent granting and examination method is provided by the EPC for inventors, thus saving inventors expenses and time of applying to individual patent national agencies [49]. However, a patent is subject to each designated nation's laws once the patent is granted by the EPO. Thus, in the unpredictable field of ethical exclusion, the advantages of filing with the EPO depend mostly on how a patent law is interpreted by each nation [49]. In addition, since the EPO is not a party to the EU, the European Court of Justice may not review decisions made by the EPO. However, the European Court of Justice remains the ruling authority regarding the conformation of nation-states to European directives. Hence, patent applications related to stem cells are best directed to national patent agencies in order to ensure timely and reliable protection [49]. Significant concerns and doubts are still being expressed regarding the interpretive and uncertainty caused by the moral exclusion clauses [48-50]. Experts thought that an absolute and inflexible framework would be created due to the inclusion of particular exempted technologies, binding regulators to moral descriptions that do not reflect continuing change in the views of society regarding what is moral and what is not. Furthermore, legal scholars argue that patent examiners would not have the relevant expertise required to assess an invention's morality since these examiners mostly are grounded in technical and scientific knowledge. In addition, the job of determining the extent of moral exemptions while keeping the sovereignty of member states in a diverse and pluralistic Europe represents a troubling constitutional and legal challenge [48-50].

Ever since the adoption of the directive, diverse interpretations have been adopted by European courts and patent offices regarding the meanings in the phrasing of restrictions on industrial and commercial uses of human embryos [51]. Some

entities, such as the UK Patent Office and the Swedish Patent Office, have adopted a permissive interpretation of the directive while others, such as the EPO, German Federal Patent Court, and the European Group on Ethics (EGE), have imposed a restrictive policy on the basis of Articles 5 and 6 [51].

An example of a case in which the EPO revoked a patent related to stem cells involved a patent by inventors Peter Mountford and Austin Smith; it was issued to the University of Edinburgh in 1999 and revoked by the EPO in 2002 [52]. A number of claims in the patent are related to selection, isolation, and proliferation of transgenic animal stem cells [53]. The Opposition Division was appointed by the EPO board to review the University of Edinburgh patent and came to the conclusion that the patent breached Article 6 (2-C), namely, the ban on the use of human embryos for commercial or industrial purpose. The Opposition Division argued that the law should be interpreted broadly in order to include not only the ban of commercial or industrial utilization of human embryos but also to encompass a ban on any human embryonic stem cells retrieved from the destruction of human embryos. Thus, the University of Edinburgh patent is void [52]. This resolution by the Opposition Division was made despite the lack of a standardized moral approach in Europe regarding human embryonic stem cells. The interpretations made by the Opposition Division also prevent granting patents for every downstream derivative, including human embryonic stem cell lines whose derivation required the embryo's destruction. These decisions made by the Opposition Division are different from previous opinions voiced by the EGE, which argued that any human embryonic stem cells adapted for potential healing purposes should be considered patentable with disregard of the source. The Opposition Division described the EGE views as inconsistent and riddled with logical flaws, in addition to being contrary to current directives and patent laws (European Patent Office Opposition Division, 2003) [52].

While the EPO has adopted a broad interpretation, as shown in its decisions, it is in contrast to the UK patent office, which has a different and narrower interpretation of the directive. The UK patent office has differentiated between stem cells that are able to develop into an entire human body (totipotent cells) and stem cells that are not able to develop into an entire human body (pluripotent cells). The UK patent office argues that since pluripotent cells do not have the potential to develop into an entire human body, they therefore can be patented [54]. The UK patent office also allows patenting differentiated types of laboratory-derived human embryonic stem cells. On the other hand, the UK patent office has encompassed totipotent stem cells under Article 5 (which bans patenting human body at different development phases) and prevented any kind of patenting related to such stem cells. Furthermore, patents will not be granted by the UK patent office for processes to attain cells from human embryos, which the patent office believe falls under Article 6, which prevents the commercial or industrial use of embryos [54]. Even with opposition to human embryonic stem cells research in UK, the UK patent office reached this consensus by taking into account the legislative framework in addition to concurring views from legislative, independent, professional, and other bodies that are accommodating of such research [54].

Due to the permissive regulatory environment in the UK regarding embryonic stem cell research patents, Geron and WARF have decided to patent their products in the UK through the UK patent office instead of doing so through the EPO. They already have filed for file both introductory and ensuing inventions, which include claims on differentiated cells made from embryonic lines [55]. A Delphoin database search for UK and US patents held by Geron and WARF was carried out for human embryonic stem cell patents in the UK. The search showed several discoveries, which includes somatic stem cells (neural and hematopoietic stem cells), progenitor cells, embryonic cell subtypes, and terminally differentiated stem cells (oligodendrocytes, dopaminergic neurons, and cardiomyocytes, hepatocytes, and β islet cells) [36].

In Sweden, the Swedish Patent and Registration Office has an interpretation that is more similar to the UK patent office than to the EPO. In 2004, a WARF patent application claiming hematopoietic cells derived from human embryonic stem cells was granted by the Swedish Patent and Registration Office on the grounds that it did not require recurring use of human embryos [36]. In 2003, the same patent was rejected by the EPO even though the claims were not related to human embryonic stem cells but to *in vitro* differentiated stem cells. The EPO made this decision since such cells at that time could not

be obtained from sources other than human embryos [55]. The EPO's policy regarding embryonic stem cells is not altogether clear, even though this decision is consistent with the ruling in the Edinburgh case. On the other hand, the EPO already has granted at least one patent on derivatives of embryonic stem cells. The patent was on neural precursor cells and it was granted to Oliver Brüstle by the EPO in 2006. This patent originally was issued to Brüstle by The German Patent Office in 1999 [56]. However, this patent was challenged by Greenpeace and then annulled by the German Federal Patent Court in 2006, on the grounds that it is not patentable based on moral grounds since the neural precursor cells could not be obtained with the need to destroy a human embryo [57]. At the moment, the EPO patent for Brüstle's neural precursor cells is being challenged by Geron, which is arguing that the patent violates the directive's morality clause [57]. Brüstle argues that "It's crazy that you are allowed to work on some human embryonic stem cell lines in Germany and develop them for clinical purposes, but patenting your methods is deemed to be contrary to public order. Consultation with the European Court of Justice will hopefully contribute to harmonization of patent practice in Europe" [57].

5. CONCLUSION

In this paper we present a study regarding the contribution of the patent on embryonic stem cell research. The paper begins with an introduction regarding the role of the patent within intellectual and industrial property in the current context, and continues with the analysis of how the patent and innovation in general influence creativity in the biological field. We analyzed the effects of overlapping research with results reflected in patent claims, which can have negative effects regarding the freedom to conduct research. The paper also discussed the emergence of a need to redistribute and trade some property rights between research centers and also between researchers. The study continues with the analysis of the situation in United States and Europe, showing the differences between existing legislation.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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