

Challenges to Human Embryonic Stem Cell Patents

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The patenting of human embryonic stem (hES) cells has produced one of the most unusual and fraught situations in the history of science, ethics, and law. This Commentary examines legal and moral challenges to three foundational patents held by the Wisconsin Alumni Research Foundation (WARF). We conclude that, in the United States, technical challenges may, paradoxically, produce a stronger patent position for WARF. In the European Union, moral challenges mean confusion for member states. We demonstrate that hES cell intellectual property will be guided and bound by a welter of moral, technical, and legal inputs, with discrete national and jurisdictional dimensions.

Introduction

In the November 6, 1998 issue of the journal *Science*, James Thomson, a professor at the Wisconsin Regional Primate Research Center at the University of Wisconsin, reported he had developed the first line of human embryonic stem cells. Penned in the typical understatement of research writing, the abstract of the research report declares, “These cell lines should be useful in human developmental biology, drug discovery, and transplantation medicine” (Thomson et al., 1998). It is unlikely that 10 years ago Thomson could imagine the torturous road his discoveries would take as they moved from the bench into broader use.

Just as human embryonic stem (hES) cells ignited a controversy about the use of human embryos for research and medicine, challenges to Thomson’s patents have emerged. Critics claim the broadness of the patents and the aggressive actions of the patent holders stifle innovation, particularly in California, where a multibillion-dollar stem cell initiative has recently begun to fund embryonic stem cell research (Murray, 2007). In the United States, opponents have attacked the patents as merely an extension of prior work, arguing they fail to meet the basic requirement that a patent be novel. Worries in Europe hark back to 1998, when the European Union (EU) adopted the Directive on Biotechnological Inventions. A clause in the Directive has been interpreted to preclude patents on inventions that required the destruction of human embryos. Each challenge is sourced by a very different locus of concern. The first seeks to invalidate the patents on technical grounds; the other would deny their claims on moral grounds. Both strategies have met with initial success.

This Commentary examines each challenge in turn and arrives at two conclusions. First, we contend that the US system, which prevents challenges until after a patent is used and then relies on the reexamination process, may, paradoxically, enhance and strengthen Wisconsin Alumni Research Foundation (WARF)’s patent position and serve to increase its patent estate. Second, the European Patent Office (EPO)’s current bar on hES cell patents illuminates a complex patent protection picture inasmuch as EU member states retain a degree of autonomy over the implementation of moral exclusions. A closer look at Europe

reveals the disjunction between the EPO and certain national policies. The consequences of the first challenge may mean further barriers for competitors in jurisdictions in which the US patents are enforced. The consequences of the second challenge may be confusion and conflict for EU states.

Challenges in the United States

On the heels of Thomson’s discovery came three foundational patents, which he assigned to his sponsoring nonprofit organization, WARF (Thomson, 1998, 2001, 2006). These patents were issued by the United States Patent and Trademark Office (USPTO) and apply throughout the United States. WARF did not file for patents in Asia but did file at the EPO and in individual European nations.

The first WARF patent, issued in December 1998, claims the general class of primate embryonic stem cells; the March 2001 patent, nearly identical to the first, directs the claims to hES cells; and the third patent describes proliferating hES cells maintained without the growth factor LIF, a protein normally expressed in the developing embryo. The patents are both bold and broad: they claim a right to all hES cell lines with the described characteristics (the “composition of matter”) and to the particular method of making them (the “process”). The composition of matter claim is the key strength: it trumps the product of any other process invention that might yield lines of hES cells. The practical consequence is that not only can WARF charge for the lines it owns, but anywhere the patent is in force it can prohibit anyone who wishes to make, use, or sell hES cell lines by any method without first negotiating a fee-based, royalty-bearing license. Two licensing strategies lie at the heart of the current controversies. Early on, WARF adopted what some considered an unusually aggressive and restrictive policy toward educational and scientific institutions, which slowed distribution of cell lines and cast a shadow over the ability of researchers to advance knowledge. In the commercial sphere, WARF’s most prominent agreement is with Geron, which has an exclusive license to develop therapeutic and diagnostic products from hES cell-derived neural, pancreatic, and cardiac cells. While WARF licensees can research these fields, any commercial potential would be subject to approval by and payments to Geron.

In 2006, The Foundation for Taxpayer and Consumer Rights, an organization involved in the passage of California's Proposition 71, and the New York-based Public Patent Foundation voiced concern about the patents' broad reach, WARF's tough licensing stance, and its public pronouncements that it would extract fees from any income the state might receive from discoveries coming from its \$3 billion California Institute for Regenerative Medicine (WARF later dropped the CIRM licensing demand). Attorneys asked the USPTO to revoke the Thomson patents on grounds that they overreach and that the methods described in their claims were already published in the public domain (so-called "prior art"). Several prominent stem cell researchers have supported the challenge, asserting that the primary reason that the prior art wasn't successfully applied was because researchers competing with Thomson didn't have the financial resources to apply the techniques to a human system (Holden, 2007).

In a preliminary ruling made in March, the USPTO declared all three patents invalid. It partially agreed with the challenges and found that the disclosures in Thomson's claims would be obvious to a person with ordinary skill in the art using public information available at the time of the patent application and that the claims were anticipated by prior patents. Some contend the ruling has dealt a severe blow to WARF's monopoly position, allowing researchers to more freely pursue hES cell research (Check, 2007).

Yet three facets of the reexamination cast doubt on the effectiveness of the strategy: (1) WARF can engage in a lengthy appeals process; (2) during the reexamination and appeals the patent remains fully in force; and (3) unsuccessful reexaminations can result in a stronger patent. When viewed in the context of the activities taken and opportunities lost in the years leading up to the reexamination, WARF and its licensee, Geron, may have an ironclad grip on major fields of hES cell development and commercialization, regardless of the reexamination's outcome.

Challenges to patents are not uncommon and do not always reflect an inherent weakness in the patent. The US patent system does not provide the public or outside experts with an opportunity to comment on or challenge a pending patent application. An invention is evaluated only through published literature disclosed by the applicant or information uncovered by the examiner. Once a US patent is granted, there are two methods to attack it. A business infringing on the patent, or using the invention without a license, might ask a court to declare the patent invalid. This strategy has serious drawbacks for the challenger. The challenger must invest in the use of the patented technology without knowing if it will eventually lose and be forced to pay damages and royalties to the patent holder. Additionally, the costs of the lawsuit can easily reach into the millions of dollars.

An alternative to a lawsuit is to petition the USPTO to reexamine the patent. This is far less costly and can be started before the challenger invests in research that might infringe. But reexaminations have significant drawbacks. An invalidation lawsuit features serial investigations, expert cross-examinations, and liberal rules for introducing evidence. And, the decision makers—judge and/or jury—are independent of the USPTO, which originally issued the patent. A reexamination, by contrast, presents a challenger with a limited opportunity to present evidence and no right to ask questions of the patent holder or challenge its submissions. The USPTO makes the final decision.

In general, while biotech patents may be more susceptible to challenge than patents in other fields, these challenges take a long time to resolve: the median length of time between a USPTO challenge and a resolution is 6.5 years (Graham et al., 2002). Long resolution times can favor the patent holder. A prominent example is Genentech's Cabilly II, a sweeping monoclonal antibody manufacturing patent due to expire in 2016. A 2005 reexamination resulted in a rejection of the patent's claims; Genentech appealed, and in 2007 it was again rejected. The company can appeal once more, and if it fails again, it can ask the courts to confirm the patent's validity. Last year alone the patent earned Genentech over \$100 million, giving the company incentives to delay a decision through appeals, which could drag on until well into the next decade (Waltz, 2007).

The Cabilly II case is instructive to evaluating the impact of the WARF challenge. One might think the uncertainty surrounding the challenge would promote unlicensed activity or, more dramatically, cause some licensees to stop paying royalties. We believe these scenarios are unlikely and note that they have not arisen in the context of Cabilly II. Investors are unlikely to fund companies who rely on unlicensed use of patented technologies while the outcome of a reexamination is uncertain. If a competing company successfully developed a new product utilizing the technology, and the challenge failed, the company would face an infringement claim and potentially ruinous demand for damages and future royalties. Because the Thomson patents remain in force during the course of the reexamination, WARF and Geron can continue to extract fees and royalties through licenses and sublicenses. If the licensee refuses to pay and the patent is ultimately found valid, it could lose its rights to exploit the technology (negating the value of its investment in the technology) and/or be forced to pay significant damages. In its responses to the initial USPTO action, WARF has amended and narrowed existing claims and added three new claims, distinguishing the differences between the Thomson method for deriving primate ES cells and the prior art of mouse ES cell culture methods. In its filing, WARF implied that if anything about the work is obvious it is the work's breakthrough: "the level of acclaim in the art for Dr. Thomson's invention bears witness to the fact that the isolation of primate/human ES cells represented true innovation that was not simply a small step in embryonic stem cell research" (Wisconsin Alumni Research Foundation, 2007).

Though it is difficult to predict the results of the reexamination, WARF has reason to express confidence. Most reexaminations uphold the patent under challenge. Reexaminations initiated by third parties results in cancellation of the entire patent only 12% of the time; 29% confirm it, and 59% confirm it with modifications to the claims (United States Patent and Trademark Office, 2007). The high rates of confirmations arise partially because patent holders themselves initiate 50% of reexaminations for purposes of buttressing their claims. They do this because challengers must present more persuasive evidence to a court to invalidate patents that have survived reexamination. Because challengers have less opportunity to present evidence and question a patent during reexamination, the patent holder can reasonably expect that the process is unlikely to uncover all damaging evidence. The end result is that a reexamination may serve to strengthen the position of WARF.

Our evaluation of the US patent landscape suggests that regardless of the reexamination's outcome, WARF and Geron's positions are already cemented in several fields of hES cell research and development. They have continued to file derivative and follow-on inventions, which will further establish their dominance. Even if Thomson's patents are overturned, the new inventions may be valid and present barriers to competition.

There are additional reasons to suggest that WARF and Geron will emerge from the reexamination in a powerful position even if the original patents are found invalid. Thomson's patents had the advantage of being both "first mover" technologies (capturing market share) and discoveries upstream from derivative inventions (capturing inventiveness). They were issued when the field was very young and its commercial potential uncertain. Further, WARF's early policies limited researchers' access to lines to produce inventions that might advance the field. Scientists working in the nonprofit sector often risk infringement because patent holders have little incentive to sue them. In the nascent hES cell field, even researchers willing to risk infringement could not obtain cell lines from WARF without agreeing to its licensing terms. Finally, restrictions on the use of federal funds for hES cell research restricted competition to WARF and Geron. Using their own lines and funding, their intellectual property estates continued to grow, protecting them should the Thomson patents be found invalid.

Challenges in Europe

The European response raises issues of a very different kind from the preliminary denial of the WARF claims in the US. The EU Directive on Biotechnological Inventions was adopted in 1998 to harmonize patent laws among member states. It contains Article 5, which prohibits the patenting of the human body at the various stages of its formation and development, and Article 6, which prevents patents on inventions that are contrary to "public order" or morality. Article 6 also lists inventions that are not patentable, including cloning humans, processes for modifying the genetic identity of humans through the germline, and "uses of human embryos for industrial or commercial purposes" (European Parliament Directive, 1998). The list was supposed to be illustrative of the existing consensus at the time on the type of inventions that were considered to be morally unpatentable. However, the fragmentation of national and European courts' jurisdiction over the Directive's implementation has generated considerable legal uncertainty and obscured patenting strategies in the field.

The 1973 European Patent Convention (EPC) treaty governs patents issued by the EPO. The EPC provides a uniform examination and granting process, saving inventors time and the costs of applying at individual national patent offices. However, once granted by the EPO, a patent is subject to the law of each designated state. Consequently, the benefits of filing with the EPO are largely dependent on the degree of certainty of the fate of a patent under national law, particularly in the volatile field of moral exclusions. An additional complication is that the European Court of Justice may not review decisions of the EPO, because the EPO is not a party to the EU (though it agreed to transpose the Directive's moral language into the EPC in 1999). By contrast, the European Court of Justice has the authority to rule whether national patent laws conform to the Directive—a power it has

already exercised in several cases. Therefore, applicants who file directly with national patent offices can short-circuit the legal process and secure an early advantage in attaining patent protection.

Still, considerable doubts and concerns were voiced over the uncertainty and interpretive difficulty caused by moral exclusion clauses (see Llewelyn, 1997; Crespi, 2003; Gitter, 2001). It was feared that the inclusion of specific exempted technologies would create an inflexible and immutable framework, binding regulators to moral definitions unreflective of changing societal views. Legal scholars pointed out that patent examiners, whose professional expertise is predominantly grounded in scientific and technical knowledge, would lack the relevant expertise to evaluate the morality of an invention. Neither was it clear how the EPC, which would likely implement the Directive, would interact with EU law, because the EPC provides a distinct and separate legal framework for granting patents through the EPO. Finally, the task of ascertaining the precise scope of moral exemptions while preserving the autonomy of member states in a diverse and pluralistic Europe was a formidable legal and constitutional challenge. As the turbulent implementation of the Directive unfolds, the legal complexities have crystallized on the much-disputed hES cell patents.

Since the Directive's adoption, the range of possible meanings encompassed by the wording of restrictions on commercial and industrial uses of human embryos is illustrated by different interpretations adopted by European patent offices and courts (Plomer, 2006). In a spectrum from the most permissive to the most restrictive, the UK Patent Office, the Swedish Patent Office, the European Group on Ethics (EGE), the EPO, and the German Federal Patent Court have adopted distinct but conflicting interpretations of excluded patents on the basis of Articles 5 and 6.

One notable case centers on the EPO's revocation of a stem cell patent issued to the University of Edinburgh. The patent, naming inventors Austin Smith and Peter Mountford, has several claims relating to the isolation, selection, and propagation of animal transgenic stem cells. The EPO board appointed to consider the case, the Opposition Division (OD), held that the patent contravened a rule that had been transposed directly from Article 6(2)(c), namely, the prohibition on "uses of human embryos for industrial or commercial purpose." Even in the absence of a uniform moral approach to human ES cells in Europe, the OD reasoned that the rule "... has to be interpreted broadly to encompass not only the industrial or commercial use of human embryos but also the human ES cells retrieved therefrom by destruction of human embryos" (European Patent Office Opposition Division, 2003). Importantly, the OD's interpretation excludes not only patents on direct uses of the human embryo but also patents on all downstream derivatives, including stem cell lines whose derivation required the destruction of the embryo (Laurie, 2004).

In reaching its opinion, the OD distanced itself from a prior opinion by the European Group on Ethics, which deemed patentable any hES cells modified for therapeutic or other uses including processes involving human stem cells, irrespective of source. The OD described the EGE opinion as not only riddled with "inconsistencies and logical flaws" but also as incompatible with existing patent law and the Directive and as such recommended that it should be "disregarded in toto" (European Patent Office Opposition Division, 2003).

By contrast, the broad interpretation favored by the EPO is at odds with a narrow view adopted by the UK's intellectual property office in 2003, which drew a distinction between totipotent cells—which have the potential to “develop into an entire human body”—and pluripotent cells, which cannot. According to the UK ruling, totipotent cells are encompassed by Article 5 of the Directive, which prohibits the patenting of the human body at the various stages of development. In addition, the UK patent office will not grant patents on processes to obtain cells from human embryos, which it considers to fall under the exclusion of industrial or commercial uses of embryos in Article 6. But it reasoned that pluripotent cells—which do not have the potential to develop into an entire human body—are not caught by the exclusion, and are patentable. Thus, the UK's policy permits patents on laboratory-derived hES cells and more differentiated kinds of stem cells (United Kingdom Intellectual Property Office, 2003).

In reaching this interpretation, the UK patent office took into account the fact that, while there had been some opposition to hES cell research, both the legislative framework and concurring view from professional, independent, and legislative bodies were supportive of the research (see Donaldson Committee, 2000; The Royal Society, 2000; Nuffield Council on Bioethics, 2001; House of Lords Select Committee on Stem Cell Research, 2002). Implicit in the reasoning is the arguably justified assumption that moral exemptions to patents should not conflict with a morally permissive regulatory regime on research.

The UK policy produced a permissive environment for hES cell patents, and like their strategy in the US, WARF and Geron and other entities have used the national office route to aggressively file both foundational patents and follow-on inventions, including claims on differentiated cells made from embryonic lines. Our search of hES cell patents in the UK reveals a broad range of discoveries, including embryonic cell subtypes, somatic stem cells (hematopoietic and neural stem cells), progenitor cells (osteoblasts), and terminally differentiated types (β islet cells, dopaminergic neurons, cardiomyocytes, hepatocytes, and oligodendrocytes). Patented methods included cell culture, transduction, and expansion systems. (A *Delphion* search for US and UK patents held by WARF and Geron was performed using classifiers from European Classification System [ECLA]. The classifiers included C12N5 [microorganisms, enzymes, or compositions thereof] together with either /06 [animal cells or tissues] or /08 [human cells or tissues]).

Sweden's interpretation of a WARF patent application claiming hematopoietic cells derived from hES cells is also seemingly at odds with the EPO position, and as such may emerge as another route for national-based hES cell patent strategies. In 2004, the Swedish Patent Office granted the patent on the grounds that it did not involve repetitive use of human embryos. WARF's corresponding application had been refused by the EPO the previous year despite the fact that the claims did not pertain to hES cells but to *in vitro* differentiated cells and their uses. The EPO's Examining Division (ED) considered that

...the present claims to fall under the exclusion...since the methods of the present application as well as the products derived therefrom cannot be obtained from a source other than the human embryo. For the purpose of morality assessment it is not sufficient that the objectable method is

not claimed *per se*, as long as it is the only thinkable—and workable—option of obtaining the claimed subject-matter.

(Wisconsin Alumni Research Foundation, 2004)

This decision is consistent with the ruling in the Edinburgh case. Yet the EPO's policy is not altogether clear. The Edinburgh ruling aside, the EPO has granted at least one patent on embryonic stem cell derivatives, specifically a patent on neural precursor cells. The German Patent Office originally issued the patent in 1999 to Oliver Brüstle, but the German Federal Patent Court recently annulled the patent in part in December 2006 following a challenge by Greenpeace. Though Brüstle did not disclose the origin of the embryonic lines and the methods are murine based, the court ruled that the invention was not patentable on moral grounds. The litigation and ruling centered on a hypothetical use of his invention. The patent was denied because neural precursor cells could be made from the destruction of human embryos (Grund et al., 2007). By contrast, in separate proceedings at the EPO, Brüstle was granted a corresponding patent by the EPO in March 2006. But surprisingly, Geron has emerged as the challenger. In opposition proceedings to the Brüstle patent, Geron is claiming—*inter alia*—that the patent contravenes the morality clause transposed from the Directive.

Proceedings for this challenge have been put on hold pending the outcome of WARF's appeal to the Enlarged Board of Appeal (EBA) at the EPO. WARF is seeking patent protection on primate (including human) embryonic stem cells and on methods of maintaining and using them. The questions under appeal arise from the claims, namely, that it was not possible for the skilled person to prepare and use human embryonic stem cells without using and destroying spare preimplantation human embryos. Specifically, the EPO is considering the following question: “[Do moral exemptions] forbid the patenting of claims directed to products (here: human embryonic stem cell cultures) which—as described in the application—at the filing date could be prepared exclusively by a method which necessarily involved the destruction of the human embryos from which the said products are derived, if the said method is not part of the claims”?

The much-awaited ruling on the WARF patents should at least settle some of the ongoing questions on the scope of application of the moral exemption clauses to human embryonic stem cells. However, we argue it will not resolve the latent tensions regarding the legal coexistence, overlap, and possible conflict between the multiple jurisdictional frameworks and actors vested with the power to grant and determine the validity of biotech patents in Europe. Tensions will unavoidably arise from the fragmentation over the implementation of the Directive and the diversity of moral views among European states. National patent offices are not strictly bound by the EPO's jurisprudence and may develop national policies on moral exclusions within the constraints set by the Directive on Biotechnological Inventions, as member states are under an obligation to implement the Directive. Though the EPO administers European patents, in the event of conflict or doubt over the implementation of the Directive, the European Court of Justice will be the ultimate arbiter. ECJ case law indicates that member states are likely to be granted a wide margin of discretion when interpreting moral exclusions, in deference to the diversity of moral and legal opinion about this sensitive and important scientific field.

Discussion

Europe's hES cell patent landscape exists in a fractured and conflicting legal environment. The EPO's forthcoming ruling in the WARF case is unlikely to conclusively settle the emerging tensions and uncertainty on the scope of moral exclusions on hES cell patents. Whatever the outcome of the WARF appeal, in a morally diverse Europe the default strategy for patent applicants is to file at the national level. In fact, some astute applicants have already leapt ahead of their competitors, bypassing the EPO to secure patents from strategically chosen national patent offices. To complete the legal maze, the opinions of the European Group on Ethics, which the Directive empowers to issue guidance on the ethics of biotechnological inventions at the level of basic principles, are not legally binding on the ECJ, the EPO, or the national patent offices.

While the US reexamination proceeds, the Thomson patents will undergo the more routine challenges of innovation. Prompted by moral worries of using frozen human embryos to derive new lines, new reports of alternative methods have been put forward. Most recently, a group of articles describe methods of making embryonic-like lines without embryos or eggs (see Takahashi et al., 2007; Maherali et al., 2007; Egli et al., 2007; De Coppi et al., 2007; Yu et al., 2007). Further experimentation with these alternative derivation techniques in human systems, whether driven by moral concerns or scientific curiosity, is one of the few areas in the field that may remain outside the scope of the WARF patents. While these techniques, especially those with human cells, may create inventions that fall outside Thomson's broad claims over the composition of hES cell lines, the reexamination will likely not resolve this question (Taymor et al., 2006). Moreover, even if Thomson's patents fall, scientific or commercial exploitation of hES cells will be subject to substantial patent estates developed by WARF and Geron during the drawn-out review and appeal process. It is likely that both entities will continue to file new patents and license existing intellectual property, increasing their dominance in the commercialization of stem cell technologies.

The patenting and commercialization of hES cells have produced one of the most unusual and fraught situations in the history of science, ethics, and law. hES cell intellectual property and its future impact on human health will be guided and bound by a welter of moral, technical, and legal inputs, with discrete national and jurisdictional dimensions. The complex and troubled landscape of embryonic stem cell intellectual property stands in stark contrast to the flattening world predicted by the globalization of other groundbreaking technologies.

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