Stem Cells: Intellectual Property Issues in Regenerative Medicine

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ABSTRACT

The topic of stem cells for use in regenerative medicine, especially embryonic stem cells, inspires much debate, discussion, and outrage as it slices through the very core moral values of society. These social and moral issues have, in turn, resulted in government policies that have influenced the study of stem cells in regenerative medicine.

Policies regulating stem cell research

U.S. government policies shaped over the last few decades have been buttressed by policies regulating government funding rather than attacks on the legal scope of patentability. Since 1996, U.S. appropriations bills have included the Dickey-Wicker Amendment as a rider that explicitly prohibits the use of government funds for the creation of human embryos or for research in which human embryos were destroyed or discarded. For the purpose of National Institutes of Health (NIH) funding, an embryo is defined as any organism not protected as a human subject under 45 Code of Federal Regulation (CFR). Part 46 that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. Since 1999, the Department of Health and Human Services (HHS) has consistently interpreted this provision as not applicable

to research using human embryonic stem cells (hESCs), because hESCs are not embryos as defined by Section 509. This long-standing interpretation has been left unchanged by Congress, which has annually reenacted the Dickey Amendment with full knowledge that HHS has been funding hESC research since 2001. These guidelines therefore recognize the distinction, accepted by Congress, between the derivation of stem cells from an embryo that results in the embryo's destruction, for which federal funding is prohibited, and research involving hESCs that neither involves an embryo nor results in an embryo's destruction, for which federal funding is permitted. Following President Barack Obama's Executive Order 13505 of March 9, 2009, the NIH issued further guidelines for funding hESC research.¹ The guidelines allowed for funding of research using hESCs derived from embryos created using *in vitro* fertilization for reproductive purposes and that were no longer needed for such purposes, with the caveat that the research should have

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¹National Institutes of Health Guidelines for Research Using Human Stem Cells ("Guidelines"), 74 Fed. Reg. 32170, July 7, 2009.

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scientific merit and that the embryos were donated after proper informed consent was obtained from the donor(s).²

Intellectual property *United States*

Social policy and funding issues aside, the patentability of stem cells and stem cell research tools is dictated by U.S. patent laws. Any invention must meet certain key criteria for patentability. As with all inventions, the invention must be directed to patent-eligible subject matter and must be new, useful, and nonobvious. In the United States, laws of nature, natural phenomena, and abstract ideas are not patent-eligible subject matter.

²The legality of funding for the work by the National Institutes of Health (NIH) were challenged and have been upheld by the U.S. Federal Court in *Sherley v. Sebelius*, 689 F.3d 776, 785 (D.C. Cir. 2012). See also *Sherley v. Sebelius*, 686 F. Supp. 2d 1 (D.D.C. 2009); *Sherley v. Sebelius*, 610 F.3d 69, 72–74 (D.C. Cir. 2010). *Sherley v. Sebelius*, 704 F. Supp. 2d 63, 70 (D.D.C. 2010); *Sherley v. Sebelius*, 644 F.3d 388, 390 (D.C. Cir. 2011).

With respect to the stem cells and their use in the field of regenerative medicine, the U.S. Patent and Trademark Office has recognized inventions involving stem cells as patent-eligible subject matter.

Three U.S. patents held by the Wisconsin Alumni Research Foundation (WARF) have been at the center of controversy with respect to the patenting of human embryonic stem cells.³ The patents cover the first isolation of nonhuman primate and human embryonic stem cells (hESCs) and have been challenged by the Foundation for Taxpayer and Consumer Rights (FTCR) and the Public Patent Foundation (PUBPAT).⁴ A more complete review of the WARF patent legal dispute can be found in the article published by John M. Golden.⁵ The controversies and legal disputes generated by the WARF patents arise from challenges asserting that these patents are overly broad and restrictive and inhibit researchers' access to stem cell lines due to high licensing costs.

Intellectual property protection of discoveries related to stem cells may now, however, turn on the question of patentable subject matter. On June 13, 2013, the U.S. Supreme Court issued its long-awaited decision in *Association for Molecular Pathology, et al., Petitioners v. Myriad Genetics, Inc., et al.*,⁶ addressing the controversial question of whether DNA is patent-eligible subject matter under 35 U.S.C. § 101. Drawing a line between two different forms of DNA molecules, the Supreme Court held that isolated DNA is an unpat-

entable product of nature while cDNA is a non-naturally occurring genetic sequence and is patentable under the statute.

In arriving at its decision, the Supreme Court elegantly laid out its reasoning and analysis of the issues at hand. Citing *Mayo Collaborative Services v. Prometheus Laboratories Inc.*,⁷ the court emphasized that there is a delicate balance between creating "incentives that lead to creation, invention and discovery" versus "impeding the flow of information that might permit, indeed, spur invention." Thus, an inventor can obtain a patent on various new processes and products but "laws of nature, natural phenomena and abstract ideas" are not patentable and "lie beyond the domain of patent protection." (*Association for Molecular Pathology, et al., Petitioners v. Myriad Genetics, Inc., et al.*)⁷ The court stresses "that without this exception, there would be considerable danger that the grant of patents would 'tie up' the use of such tools and thereby 'inhibit future innovation premised upon them.' " It is important to note that the court does emphasize that the "rule against patents on naturally occurring things has limits." The court relies on the standard set in *Diamond v. Chakrabaty*⁸ in which "[p]roducts of nature are not created, and 'manifestations... of nature are free to all men and reserved exclusively to none,' " to underscore the importance of maintaining such a balance. The court went on to explain that "complementary DNA" was patent eligible as it is created in the laboratory, versus "isolated DNA," which is "DNA taken from a part of the entirety of an organism's hereditary information or chromosomes."⁹

Although the issue in this case was whether isolated nucleic acids are patent eligible, the ruling underscores the court's determination to balance access to research tools for innovation versus innovation itself. How this ruling can be extrapolated to intellectual property rights in regenerative medicine remains to be seen,¹⁰ since a stem cell is a sophisticated, living organism and thus more complex than an isolated string of nucleobases. Much, however, may depend on the extent of human manipulation of the stem cell in the laboratory and how the subject matter of the discovery can be translated into meaningful claims in a patent. It is likely that any claims that are directed to an isolated stem cell identified, for example, by biomarkers, could be construed by a well-reasoned court as a product of nature, and as such would be ineligible patent subject matter. The extent of "manipulation" required by this standard will depend on how removed from the "natural state" the isolated stem cell is, bearing in mind the unique abilities of stem cells.

As always, it is recommended that researchers work very closely with their patent practitioners when drafting a patent application to ensure that their products are outside of the nature exception, that the claims sufficiently describe their invention, and that the invention is novel and nonobvious.

³U.S. Patent Nos.: 5,843,780; 6,200,806; 7,029,913.

⁴In April 2007, the USPTO revoked the patents on the grounds that Thomson's work was obvious in the light of previous scientific work and thus unpatentable. In 2008, the Patent Examiner reversed the revocation order and upheld the patent claims. The April 28 BPAI decision is the latest episode in the patents' controversial history.

⁵*Journal of Law, Medicine and Ethics*, Vol. 38, No. 2, pp. 314–331, 2010, University of Texas Law, Public Law Research Paper No. 198.

⁶*Association for Molecular Pathology, et al., Petitioners v. Myriad Genetics, Inc., et al.* 569 U.S. __ (2013).

⁷*Mayo Collaborative Services v. Prometheus Laboratories Inc.*, 4 566 U.S. __ (2012).

⁸*Diamond v. Chakrabaty* (447 U.S. 303, 309) (1980).

⁹According to the court, the BRCA1 and BRCA2 genes were merely separated from their "surrounding genetic material," which was "not an act of invention." To exemplify this point, the court relied on the precedent set by *Diamond v. Chakrabaty*. Unlike in *Chakrabaty*, where modified bacterium were deemed patentable products of human ingenuity, the court reasoned that Myriad's isolated DNA did not possess any "markedly different characteristics" from the nucleotides making up the BRCA1 and BRCA2

genes as they exist in nature. Rather, the opinion likened the Myriad case to *Funk Brothers Seed Co. v. Kalo Inoculent Co.*, 333 U.S. 127 (1948), which illustrated that mere discovery of a natural principle does not, in and of itself, render a composition of such naturally occurring products patentable under § 101.

¹⁰On July 2, 2013, Consumer Watchdog requested the Court of Appeals for the Federal Circuit to apply the "product of nature" analysis based on *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al.*, to claims covering human embryonic stem cells. This appeal arises from the Patent Trial and Appeal Board's decision in *Consumer Watchdog v. Wisconsin Alumni Research Foundation (WARF)* confirming the patent eligibility of claims in WARF's U.S. Patent No. 7,209,913 covering a "replicating *in vitro* cell culture of human embryonic stem cells."

Europe

In the European Union (EU), the EU Biopatent Directive (Directive on the Legal Protection of Biotechnological Inventions 98/44/EC) was meant to assure harmonized patent protection for biotechnological inventions in the EU. The directive, however, also contains exemptions from patentability. Art. 6(1) of the directive states that “patents contrary to order, public and morality are excluded from patentability.” To provide national courts and patent offices with guidance on interpreting this clause, an illustrative list of examples were incorporated in Art. 6(2) of the Biopatent Directive. One example of major relevance to stem cell-based inventions is Art. 6 (2) (c), which states that “uses of human embryos for industrial or commercial purposes” shall be excluded from patentability. The terms “human embryo” and “industrial or commercial purpose” is not defined in the directive, leading to what can amount to much confusion and differences in the implementation of the directive among EU member states.

This directive was tested on November 27, 2012, when the German Federal Supreme Court rendered a decision in *Brüstle vs. Greenpeace Case*, Docket No. X ZR 58/07, as to whether neural precursor cells, which originate from human stem cells, are patentable or not. In the way of background, in 1997 Oliver Brüstle, a German scientist, filed a patent application in the German Patent and Trademark Office (DPMA), and a patent was granted by the DPMA on April 29, 1999, as German Patent No. 197 56 864. The subject matter of the patent was directed to the protection of neural precursor cells, a procedure to cultivate these cells and the usage of these cells in therapies for neural defects of humans and animals. According to the patent, these neural precursor cells were obtained from embryonic stem cells. The embryonic stem cells in turn could be obtained from an embryo in an early stage of development, which leads to the destruction of the embryo.

In October 2004, Greenpeace filed a nullity action against the patent with the German Federal Patent Court with respect to claims on subject matter directed to neural precursor cells derived from human embryonic stem (ES) cells. The nullity action was exclusively based on the reasons of offense against public policy and common moral principles, as it leads to the destruction of human embryos. Section 2, paragraph 2, No. 3 German Patent Act of February 28, 2005, sets forth that a patent shall not be granted for the use of human embryos for industrial or commercial purposes. This regulation corresponds to and implements German law Article 6, paragraph 2 of the directive 98/44/EC on the legal protection of biotechnological inventions. In accordance with this argument, the German Federal Patent Court ruled in December 2006 that the patent was mainly invalid (German Federal Patent Court, decision of December 5, 2006, case no.: 3 Ni 42/04, *Greenpeace vs. Oliver Brüstle*). The patent owner, Oliver Brüstle, filed an appeal in the German Federal Supreme Court, which suspended the case and requested a preliminary ruling by the Court of Justice of the European Union (CJEU) (German Federal Patent Court, decision of December 17, 2009, case no.: X ZR 58/07) on the interpretation of the term “human embryo” and the term “use of human embryos for industrial or commercial purposes.”

Central to *Brüstle vs. Greenpeace* (CJEU C-34/10) was the interpretation given to Article 6(2)(c) of Directive 98/44/EC (the Biotechnology Directive), the Court of Justice of the European Union (CJEU), which excludes *inter alia*, the patentability of inventions involving “the use of human embryos for industrial or commercial purposes.” The court held that the concept of “human embryo” must be understood to encompass any ovum once fertilized, including whether created by transfer of a nucleus from another mature cell or stimulated to cell division by parthenogenesis. The court went on to state that the exclusion from patentability concerning the use of human embryos for industrial or commercial purposes set

out in Article 6(2)(c) of the Biotechnology Directive also covered the use of human embryos for purposes of scientific research. The CJEU voiced one exception, that the use of a human embryo for therapeutic or diagnostic purposes that were applied to the human embryo and were useful to it is *prima facie* patentable. Lastly, the court found that where an invention does not itself “use” human embryos but relates to “a product whose production necessitates the prior destruction of a human embryo or a process that requires a base material obtained from such destruction,” that invention would not be patentable as it would constitute use within the meaning of Article 6(2)(c) of the directive.

In accordance with the interpretation of the CJEU, the German Federal Supreme Court reversed the judgment of the German Federal Patent Court and maintained that the Brüstle patent would be invalid with respect to claims encompassing neural precursor cells, which had been obtained by destroying embryos. The German Federal Supreme Court upheld the claims of the patent related to other methods of obtaining neural precursor cells without the destruction of an embryo. The German Federal Supreme Court held that the only relevant standard to determine whether the patent violated Sec. 2, paragraph 2, No. 3 of the German Patent Act was whether there are ways to harvest stem cells from a human embryo without destroying it, irrespective of whether such ways or methods are actually disclosed in the patent (p. 13 *et seq.*).

The German Federal Supreme Court reached the following conclusions regarding the term “embryo.” The court held that the harvesting of cells from embryos that have fully and finally ceased to develop further is not a “use of human embryos” within the meaning of Sec. 2 para. 2, No. 3 PatG (p. 14). The court further concluded that human stem cells harvested without destroying an embryo are not to be regarded as embryos themselves under the law because they lack the potential

of setting in motion the development of a human being.

The ban on patenting embryonic stem cells in the EU is currently being challenged by groups in Britain who have been joined by a high court judge who has asked the CJEU to clarify its decision to prevent the patenting of stem cell research involving the use and destruction of human embryos. These groups claim that the ban is deterring investment in Europe while competitors in Asia are able to continue unhindered in their research of regenerative medicine based on embryonic stem cells.

Summary

As the intellectual property (IP) landscape currently stands, hESCs and pluripotent stem cells and methods of making or using such cells are patentable in the United States but not in the EU. However, with the recent developments in the United States, it may not be long before vocal segments of society push for a reexamination of patent eligible subject matter with respect to isolated stem cells. At this juncture, research institutions and companies should reexamine their IP, regulatory, and commercial strategies on a jurisdictional basis and remain abreast of current patent law

developments. In certain jurisdictions, nondisclosure mechanisms of confidentiality and trade secrets may be the only options available in the protection of innovations in the stem cell field. Whatever the outcomes, the field of regenerative medicine will continue to be influenced by both government policies and court rulings in respective jurisdictions.

Author disclosure statement

No competing financial interests exist.