

# JOURNAL

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of the Association of University Technology Managers™

Volume XVIII Number 2

Fall 2006

***Patenting, Licensing, and Social Responsibility***



# Human Embryonic Stem Cells: A Review of the Intellectual Property Landscape

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## Abstract

It is hard to have missed the controversy surrounding human embryonic stem cell (hESC) research. Researchers who are interested in this field believe that hESCs' potential to cure many previously incurable diseases, such as type 1 diabetes and neurodegenerative disorders, outweigh the concerns raised by critics who object to hESC research because a human embryo is destroyed during the creation of hESC lines. For those who are interested in research on hESCs, there is also a complicated intellectual property landscape to navigate. This paper will review the major patents in the hESC field and their availability for both research and commercial purposes. This paper will also review the recently released intellectual property policy put forth by the State of California that accompanies its funding of stem cell research. California's policies will likely serve as the model for other states' funding of stem cell research. The goal of this paper is to clarify the intellectual property landscape so that researchers and university intellectual property professionals can have a basic understanding of what barriers exist to research and commercialization and how to overcome such barriers in this exciting field. The good news is that, for most uses of hESCs, rights are available through licensing.

## Setting the Stage: Some Science and Some History

It is impossible to make sense of the intellectual property landscape surrounding hESCs without first understanding a little about the biology of hESCs and some of the history and politics that have influenced the funding of research on hESCs in the United States.

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*This article was originally written for the Journal of the Association of University Technology Managers™ and appears in the Fall 2006 issue, Volume XVIII Number 2, pages 1–13. Copies of the complete AUTM Journal® are available for purchase. Visit [www.autm.net](http://www.autm.net) or contact AUTM headquarters at [info@autm.net](mailto:info@autm.net) or 847/559-0846 for details.*

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### What Are hESCs?

Stem cells are the cells in the body that can divide and produce other types of cells. They serve to build and replenish the body's tissues and organs. They also are able to make every cell type and, therefore, every tissue in the body (this quality is called *pluripotency*). They are like the fertilized egg, which is a single cell that gives rise to every cell type in the body. That means that hESCs have the potential to be used to make replacement tissues and organs to cure disease.

Human embryonic stem cells are made from fertilized eggs that have divided a number of times to form a cell mass called a *blastocyst*; hESC lines are derived from single cells that are removed from the blastocyst. This process destroys the blastocyst, which had the potential to develop into a human being. Critics equate this destruction of the blastocyst with the taking of a human life. Proponents counter that the hESC lines that exist have been made from fertilized eggs, left over from in vitro fertilization, that were going to be destroyed anyway. These blastocysts are made outside of the body (in vitro) and are not implanted in a uterus at any time.

There are many types of nonembryonic stem cells called adult stem cells. Adult stem cells exist in many tissues, and they make the cells that tissues use to replenish themselves. For instance, hematopoietic stem cells are cells that produce blood cells. Unlike pluripotent hESCs, adult stem cells are differentiated, which means they can form the cells of certain tissues, but can no longer form all of the cell types of the body. For example, hematopoietic stem cells can make the various blood cell types, but they cannot make skin. The only currently approved human stem cell therapies use adult stem cells. The most well-known example is bone marrow transplants.

Given this complicated political and moral backdrop, why do researchers want to use hESCs rather than adult stem cells? Many scientists believe that hESCs have the greatest potential for human therapeutics because of their great flexibility to further differentiate into every possible cell type. In addition, it is not clear that adult stem cells exist in all tissues; for example, adult stem cells have not been found in the pancreas.

### Funding of hESC Research in the United States

The political history of federal funding of hESC research has shaped the intellectual property landscape. In the United States, the federal government funds almost all of the basic research in the life sciences, mainly through the National Institutes of Health (NIH). From 1980 to 2001, there was a moratorium on federal funding of research on human embryos, which precluded funding of research on hESCs. In the 1990s, political pressure grew from the scientific community and patient advocacy groups to change this rule and to permit funding of research on hESCs. In response to this pressure, President George W. Bush released a policy<sup>1</sup> in 2001 that permits limited federal funding for hESC lines. The limitation was that federal funding could be used only for research on hESC lines in existence at the time the policy was announced. This compromise gave scientists permission to do hESC research, but prohibited federal funding for the creation of or research on new hESC lines. There is no prohibition in the United States on research on hESCs, but without federal funding, the ability of scientists to conduct basic research in this area is severely limited. Basic research on hESCs is continuing outside of the United States in countries that do not have similar restrictions. For example, Great Britain and Israel are emerging as leaders in research on hESCs. Against this political backdrop, some states, such as California, have entered the arena of funding research on hESCs.

### Patents on hESCs

The concept that regenerative cells, such as stem cells, exist has been around since the early 1900s, and many different researchers have worked on aspects of understanding stem cells. However, James Thomson, a professor at the University of Wisconsin, was the first to isolate hESCs. As the first to do so, he was awarded a very broad patent, US Patent No. 6,200,806, which issued on March 13, 2001, and is assigned to the Wisconsin Alumni Research Foundation (WARF). A related patent application was filed in Europe and is on appeal in the European Patent Office. There are no related patents pending in Asia, Australia, or Israel.

The patent covers three aspects of hESC: an isolated culture of hESC, the method of isolating hESC cells, and the cell lines derived from such a method. Below is a review of the actual patent claims. This patent is not

limited to any specific tissue types, nor is it limited to any particular use of hESCs, so it could be read to cover every type of hESC, and any research, diagnostic, or therapeutic use of hESCs. In effect, any use of hESCs, of any type, for any purpose, may fall under this patent. This patent, along with two other related Thomson patents, has recently been challenged by two public interest groups in California, the Foundation for Taxpayer and Consumer Rights and the Public Patent Foundation. The groups have filed a request for reexamination of the issued patents with the United States Patent and Trademark Office (USPTO). If the reexamination request is granted, the patent office examines the patent claims again in light of new information. The basis of this challenge is that the discovery was not novel. It is too early to predict whether this challenge is valid or will be successful.

The first claim of this patent is to the actual hESCs themselves, and it is directed toward pluripotent hESCs, which are the kind of hESCs that can turn into any human tissue. The actual claim reads: “Claim 1: A purified preparation of pluripotent human embryonic stem cells which (i) will proliferate in an in vitro culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.”

The next claim of major interest is directed toward the method of isolating hESCs. Claim 9 reads: “Claim 9: A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of (a) isolating a human blastocyst; (b) isolating cells from the inner cell mass of the blastocyst of (a); (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed; (d) dissociating the mass into dissociated cells; (e) replating the dissociated cells on embryonic feeder cells; (f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and (g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic hESC line.”

And finally, Claim 11 speaks to the cell lines derived from such a method: “Claim 11: A cell line developed by the method of claim 9.”

#### Availability of the Thomson Patent

Thomson is a researcher at University of Wisconsin, and he consequently assigned his rights in this patent to the Wisconsin Alumni Research Foundation (WARF), its technology transfer organization. WARF has formed a subsidiary named the WiCell Research Institute Inc. (WiCell) to handle the licensing of its hESC patents and materials. All licensing is done by WiCell. WiCell licenses both the patent rights and the hESCs developed by Thomson. The hESC lines developed by Thomson were made before Bush's policy on hESCs was released and are, therefore, approved for research using federal funding.

WiCell signed a memorandum of understanding (MOU) with the Public Health Service (PHS), US Department of Health and Human Services, on September 5, 2001, in which WiCell granted rights to PHS-funded researchers (with limitations to be discussed below). PHS includes the NIH, which funds most of the life science research in the United States. The MOU covers access to the hESC lines developed by Thomson (WiCell materials), access to the patent rights for use with the WiCell materials, and for use with other approved hESC lines.

#### *Terms of the MOU: Access to Thomson Patent Rights*

The patent rights are available, free of charge, to researchers funded by PHS for use only on hESC lines approved by the government. Such rights are available as well for third-party suppliers of approved hESC lines provided to PHS researchers. In effect, WARF has agreed not to enforce its patent against academic researchers who wish to work on the approved hESCs.<sup>2</sup>

There are some limitations to this grant of rights. The first is that researchers cannot do work for commercial purposes or for the direct benefit of a research sponsor, unless such sponsor has independently received rights from WiCell. Third-party suppliers of hESCs (that is, the owners of the other approved hESC lines) are granted the right, free of charge, to distribute their hESCs to PHS-funded researchers, provided that such suppliers may not directly or indirectly receive intellectual property rights in exchange for the supply of materials. Very importantly, WiCell does not ask for any reach-through rights to discoveries made by academic researchers. Universities are expected to sign a MOU directly with WiCell.<sup>3</sup>

### *Terms of the MOU: Access to Thomson Cell Lines*

The WiCell materials, which are approved under the government's policy for federal funding, are available to PHS-funded researchers for a nominal fee (as of this writing, the fee was \$500 per cell line, recently reduced from \$5,000). These cell lines come with some restrictions.

The cell lines may not be used for diagnostic or therapeutic purposes and may only be used in noncommercial research, which means they may not be used in industrially sponsored research, unless the industrial sponsor has a separate license from WiCell. There are some restrictions on the use of the cells to prevent the cells from being turned into embryos. Universities are required to certify their compliance with these rules annually, to share the subject of their research, and to share small amounts of new materials, free of charge, with WiCell.

### *Other Approved hESC Lines*

Under the MOU, third-party suppliers of hESCs are granted rights to transfer the materials to PHS-funded researchers, so long as the terms of the transfer are no more onerous than WiCell's terms. That, in effect, has made the terms of the other hESC suppliers nearly identical to WiCell's.<sup>4</sup>

### *Creation of New hESC Lines*

Researchers who wish to create new hESC lines are prohibited from doing so under federal funding and must get funding from other sources, such as companies, foundations, nonfederal government agencies, or private donations. In these cases, the rights to the Thomson patent are not granted under the MOU. Below are the means of access to the Thomson patent for such work.

### *Commercial Funding*

Researchers who wish to work on hESCs under commercial funding can get access to the Thomson patents if the commercial funder obtains rights directly from WiCell. Research-use rights (excluding any preparation for therapeutic use and any diagnostic use) are available for all cell types on a flat-fee basis; the fee is based on company size.

For rights to commercialize hESCs, nonexclusive licenses are available. These are based on applications, i.e., sale for research use, diagnostic or

therapeutic use, and cell type. For diagnostic and therapeutic uses, the important fields of heart, pancreas, and nerve are not available because they are exclusively licensed to Geron (more detail below).

*Other Sources of Funding: Foundations, Private Donation, State Funding*

Funding for hESC research is available from a number of noncommercial sources such as foundations, private donations, and state governments. Institutions that wish to get access to the patent rights for research in these areas must get the rights directly from WiCell. WiCell has granted a number of such research licenses on terms similar to those in the MOU.

*Geron's Rights*

Geron funded some of Thomson's work that led to the patents discussed above. As a research funder, Geron was offered an option to a royalty-bearing exclusive license to the patent rights developed under its funding. These are standard terms of industrially funded university research. Through exercising this option, Geron received exclusive rights for diagnostic and therapeutic uses in the fields of heart, pancreas, and nerve. Geron also has nonexclusive rights to a number of other cell types. Geron has the right to sublicense its exclusive rights.<sup>5</sup>

*Other Patents on hESCs*

Many other researchers and companies other than WARF have been active in the hESC field.<sup>6</sup> The other patents contain limitations that make them less broad in scope than the Thomson patent. For example, Vanderbilt University owns US Patent No. 5,453,357, which claims a composition comprising (a) pluripotential embryonic stem cells and (b) fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor. To fall under the claims of this patent, a product would have to include both the stem cells and the four named components in the media. Similar limitations are common in other hESC patents, such as Geron's patent, US Patent No. 6,642,048, and Amrad Corp. Ltd.'s patent, US Patent No. 5,166,065. The Johns Hopkins University's patent, U.S. Patent No. 6,090,622, is limited to human embryonic germ cells. Other patents, of which there are many, are tissue specific. In conclusion, the other hESC patents are narrower than the WARF patent and so it is possible to

work in the hESC field without needing rights to many of these patents. Of course, a researcher should check whether any particular product, or method, falls under the claims of specific hESC patents.

### *The Situation in Europe*

To date, patents on hESCs are not permitted in Europe. The European Patent Office (EPO) is required to consider moral issues in the granting of patents. In 1999, the European Patent Commission (EPC) adopted a piece of legislation from the EU Biotech Directive in its EPC Implementing Regulations, creating what is called Rule 23d(c)EPC, which reads, “uses of human embryos for industrial or commercial purposes” are to be excluded from patentability. The EPC has interpreted this rule very broadly and has rejected all patents relating to hESCs, including methods of making and using hESCs and products derived from hESCs, such as differentiated cells. The Thomson patent has been rejected on these grounds and is on appeal. It should be noted that some national offices in Europe are taking a narrower view of Rule 23d(c)EPC. The United Kingdom patent office, for example, is granting patents to pluripotent stem cells, but prohibiting patenting of totipotent stem cells and the processes of obtaining hESCs. The German patent office is also taking a narrower view of the EPC ruling. As a strategy, some companies are filing directly in the national offices and bypassing the EPO.

The EPC’s refusal to grant patents on hESCs in Europe means that anyone is free to practice any stem cell invention in Europe; however, there is also no market protection for hESC products in Europe. Given the appeals pending for the Thomson and other patents, the situation in Europe will likely change and is worth watching.

### *Summary of hESC Patents*

WARF owns a very broad patent in the field of hESC, potentially dominating both research and therapeutic uses, in all therapeutic fields, using all cell types. For PHS-funded researchers who wish to work on hESCs approved by the federal policy, the patent rights are available, free of charge, through WiCell. For academic researchers who wish to work under commercial sponsorship, to develop new hESC lines, or perform research on nonapproved hESC lines, the commercial sponsor must get the rights from WiCell;

they are available. For academic researchers who wish to use other non-commercial sources of funding to create novel cell types, such as foundations, gifts, or state governments, the rights are available directly from WiCell, subject to negotiation.

For companies that wish to do research on hESCs, the rights are available for a flat fee from WiCell. For companies that wish to commercialize hESCs, the rights are available on a nonexclusive basis from WiCell (terms not publicly available), but the fields of heart, pancreas, and nerve are not available because they are exclusively licensed to Geron, which may or may not be willing to offer a sublicense. This is critical because these hESCs include ones that might lead to regeneration of nerves, cure diabetes, and/or treat heart disease.

For universities that wish to license their hESC patents and are concerned about freedom to operate for their licensees, it appears that there are very few barriers outside the fields Geron has rights to since WiCell is making the rights available to companies.

#### Other Funding of hESC Research: California

In response to the federal restrictions on funding of hESC research, a number of states have stepped into the void. The first was California. On November 2, 2004, the residents of California passed California Proposition 71, which established the California Institute for Regenerative Medicine (CIRM) to disburse up to \$3 billion in state bond funds to conduct hESC research at California universities and institutions and construct research facilities. Many other states have proposed legislation to fund hESC research, including New Jersey and Massachusetts. None yet rival the size or commitment of California.

On February 10, 2006, CIRM released its Intellectual Property Policy for Non-Profit Organizations.<sup>7</sup> This critical document lays the groundwork for how inventions arising from CIRM funding will be handled, and it is likely to be the model that other states follow as they begin funding basic research. Terms for commercial recipients have not yet been released.

CIRM has put together an excellent, well-thought-out, and reasonable intellectual property policy. Its policies will likely encourage the commercialization of hESC research while not putting excessive restrictions on recipient institutions. Like Bayh-Dole, CIRM allows universities to control

the commercialization of inventions made under CIRM funding. Because the policies are compatible with those governing commercialization of federally funded research, universities and other nonprofits will be able to manage the CIRM funding within their existing structures.

#### CIRM Specifics

##### *Ownership of Intellectual Property*

Recipient institutions will own, patent, and be able to grant licenses to inventions made under CIRM funding.

##### *Financial Aspects*

CIRM requires that recipient institutions share some of their revenue with the State of California. In particular, for a given invention, for any income more than \$500,000 (cumulative), the institution must share 25 percent with CIRM, after the inventor's share is distributed. This allows CIRM to share directly in blockbuster patents, but relieves universities of the burden of sharing revenue from smaller inventions. Interestingly, WARF has interpreted this revenue sharing as commercial use and has approached CIRM to request a share of this revenue as a licensing fee.

##### *Access to Research Result*

Recipients are required to share biomedical materials for research purposes in California within sixty days of request (with a few, very limited exceptions).

##### *Exclusive Licensing*

The intellectual property policy emphasizes nonexclusive licensing, but recognizes that exclusive licensing is necessary for investment in development and so does not directly discourage it.

##### *Price Controls*

Exclusive licensees must plan to provide access to resultant therapeutics and diagnostics for uninsured California patients at federal Medicaid prices.

### CIRM Concerns

The policies listed above will allow nonprofits to manage their intellectual property just as they do for federally funded research and industrially funded research. CIRM does not ask for control of intellectual property or control of licensing, nor does it ask for unreasonable financial returns. None of these policies will act to impede commercialization of CIRM-funded research; however, there are a few aspects of the policy that cause concern. These are listed below.

#### *Research Exemption*

All California research institutions, both for profit and nonprofit, are granted a research exemption to use any inventions developed under CIRM funding. This means that CIRM-funded inventions cannot be enforced against any California institutions, including companies, using the invention for research purposes. This will surely simplify certain types of research by removing the need for licenses; however, it also precludes market exclusivity for research products and services. There are certain research products and services that need the incentive of market exclusivity to attract investment in product development and marketing. If California becomes a hub for hESC research as a result of CIRM funding, the research exemption may destroy important markets for certain research products and services and will potentially discourage commercialization of an important category of products in the hESC field.

#### *March-in Rights*

The State of California has some very broad, and worrisome, march-in rights: “CIRM shall have the right to require the grantee organization, or exclusive licensee...., to grant a nonexclusive, partially exclusive or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable.... if the CIRM determines that such an action is required....”<sup>8</sup>

It can be required if:

1. Grantee organization or licensee has not made responsible efforts in a reasonable time to achieve practical application of a CIRM-funded patented invention

2. Licensee has failed to adhere to the agreed-upon plan for access to resultant therapies
3. To meet requirements for public use when the requirements have not been satisfied
4. To alleviate public health and safety needs which are not reasonably satisfied by the grantee organization or licensee and which needs constitutes a public health emergency

These march-in rights are so broad that it is conceivable that they will discourage investment in important therapeutic products because of the risk of loss of exclusivity after investment. For example, look at reason No. 1: If the licensee has not brought any invention to fruition in a “reasonable time,” CIRM can take the rights away. How will a reasonable time be determined for an area as uncertain as hESC therapy? Reason No. 3 is also quite ambiguous. There is no definition of “public use requirement,” nor are there examples of what it might mean to say it has not been satisfied. Reason No. 4, “to alleviate public health and safety needs,” could easily lead to a situation in which a patient advocacy group demands access to an invention, and the political pressure is such that CIRM agrees and marches in. While such a march-in might (or might not) be the best approach in that individual case, such a use of a march-in will scare off future investors. Such broad march-in rights, held by a state government, might discourage investment in the very inventions they hope to see commercialized. These are extremely high-risk, early-stage investments, and strong market protection will be needed to convince investors to fund such companies and develop hESC therapies. The impact of these march-in rights will hinge on whether they are invoked. If they are not invoked over a long period of time, investors will feel more confident, as they do with federal march-in rights in federally funded inventions, which have never been invoked, and, thus, do not discourage investment.

Aside from these concerns, however, this policy is very good for university technology transfer and development of early-stage research. And, as in many things, California often leads the nation. As more states move into the funding arena, the CIRM policies will serve as a template and will likely benefit recipients of other state funding.

## Conclusion

Over time, the intellectual property landscape around hESCs has become clearer. WARF, working with the PHS, has set up a system in which the rights to the Thomson patent are available, via license, in almost all fields with the exception of a few therapeutic areas, for use with government-approved hESC lines and for formation of novel hESC lines. California's funding of stem cell research is moving forward, and its intellectual property policies will make it simple for nonprofits to accept CIRM funding and work within its intellectual property rules. While the future of hESCs as a therapy is still very speculative and actual treatments are far off, the intellectual property situation should not prevent this field from moving forward.

## Notes

1. The White House, "Fact Sheet: Embryonic Stem Cell Research," news release, August 9, 2001, <http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html>.
2. The memorandum of understanding is available for download at [http://stemcells.nih.gov/staticresources/research/registry/MTAs/Wicell\\_MOU.pdf](http://stemcells.nih.gov/staticresources/research/registry/MTAs/Wicell_MOU.pdf).
3. The memorandum of understanding is available on the WiCell Web site at <http://www.wicell.com/>.
4. The NIH Web site at <http://stemcells.nih.gov/> is an excellent resource to find details of each hESC line (numbered now at about twenty-two) and the details of the availability of each.
5. More information can be found on the Geron Web site at <http://www.geron.com>.
6. For an excellent review of these patents, see Robert W. Esmond and Robert A. Schwartzman, "Stem Cells: The Patent Landscape," June 2005, <http://www.skgf.com/media/news/news.148.PDF>.
7. For more information about the Intellectual Property Policy for Non-Profit Organizations, see the Web site at <http://www.cirm.ca.gov>.