EGREGIOUS ERROR OR ADMIRABLE ADVANCE: THE MEMORANDUM OF UNDERSTANDING THAT ENABLES FEDERALLY FUNDED BASIC HUMAN EMBRYONIC STEM CELL RESEARCH

> *Nothing contained herein shall be considered to be the grant of a commercial license or right under the Wisconsin Patent Rights or to Wisconsin Materials. Furthermore, nothing contained herein shall be construed to be a waiver of WiCell's patent rights under the Wisconsin Patent Rights or WiCell's property rights in Wisconsin Materials.*[1]

Introduction

The federal government designated the National Institutes of Health (NIH) to negotiate an agreement to allow researchers access to the human embryonic stem cell lines specified under federal research guidelines. The stem cell lines available in the United States are controlled by the WiCell Research Institute and, in part, Geron Corporation. On September 5, 2001, NIH and WiCell signed a Memorandum of Understanding (MOU) that granted federally funded researchers access to WiCell's stem cell lines for basic research purposes only and waived WiCell's reach-through rights on the resulting discoveries. The MOU does have the clear benefit of enabling important basic research yielding many potential medical benefits. The problem with the MOU is that after basic research, WiCell and Geron can potentially block all or selected commercial and therapeutic development and usages involving WiCell and Geron intellectual property. In essence, the federal government is funding the expanded basic research of two private companies that already have a legal monopoly on a broad set of stem cell products and methods under pre-existing patent rights, while providing no safeguards on the licensing activities of the patent holders.

What Is Human Embryonic Stem Cell Research?[2]

Human embryonic pluripotent stem cells (HEPSCs) were first isolated in 1998 by James Thomson at the University of Wisconsin at Madison. As standard in vitro fertilization creates many excess human embryos, many participants of the treatment have decided to donate their excess embryos for research purposes. Embryonic stem cells are created from the inner cell mass of a week-old human embryo created in the course of the infertility treatments. With proper culture, the embryonic stem cells

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[1] *The Memorandum of Understanding between WiCell Research Institute, Inc. and the Public Health Service*, Sept. 5, 2001, *available at* http://www.nih.gov/news/stemcell/WicellMOU.pdf.

[2] For a more detailed description of the derivation of human embryonic stem cells and the steps of stem cell research, see the NIH's educational report on stem cell research. *Stem Cells: Scientific Progress and*

can grow and divide indefinitely, with the potential to develop into almost all types of body tissues. A stem cell line is a cell population that reproduces from the original embryonic stem cell that shares its genetic characteristics. After replication in culture, cells from the cell line can be distributed to researchers.

The Legal Background for Human Embryonic Stem Cell Research

When Thomson established the first HEPSC line in 1998, Geron Corporation of Menlo Park, California, sponsored Thomson's research, as no government funding was available. Thomson was granted three patents, which are held by the Wisconsin Alumni Research Foundation (WARF). United States Patent 5,843,780 issued on December 1, 1998 and claims primate embryonic stem cells, United States Patent 6,200,806 issued on March 13, 2001 and claims a purified preparation of HEPSCs, and United States Patent 6,280,718 issued on August 28, 2001 and claims the method of hematopoietic differentiation of HEPSCs. WARF then granted an exclusive commercial license to Geron to commercialize products based on a limited six cell types of medical importance: liver, muscle, nerve, pancreas, blood, and bone.[3] WARF has recently sued to restrain Geron from extending its commercial rights in WARF's cell lines to an additional 12 derivative cell types.[4] In addition to Geron's rights under the WARF patents, Geron also has patent rights to future stem cell developments as it filed additional patents on techniques of growing stem cells and on controlling differentiation into a specific cell type.[5] WARF and other cell providers have publicly stated that they are interested in making their cells available for use in federally funded research.[6] The Wisconsin stem cell lines are currently available from WiCell Research Institute, a WARF subsidiary, to any research group that signs a Materials Transfer Agreement to use them for only basic research.

Before August 2001, the U.S. House of Representatives had already passed a bill banning cloning of human cells for research purposes. On August 9, 2001, President Bush officially announced his support for limited federal funding for human embryonic stem cell research. The conditions to gain federal funding for a quality stem cell line in existence on August 9, 2001 are that the original embryonic stem cell: (1) was gained through the informed consent of the parents; (2) the cells must have been created from excess embryos produced in an in-vitro fertilization laboratory; (3) the cells must not have

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Future Research Directions, August 6, 2001, *available at* http://www.nih.gov/news/stemcell/scireport.htm.

[3] Sheryl G. Stolberg, *Patent on Human Stem Cell Puts U.S. Officials in Bind*, N.Y. TIMES, Aug. 17, 2001, at A1.

[4] *Geron Announces Notice of Lawsuit*, Aug. 14, 2001, *available at* http://www.geron.com/pr_20010814.html.

[5] Andrew Pollack. *The Promise in Selling Stem Cells*. N.Y. TIMES, Aug. 26, 2001, at C1.

[6] Jocelyn Kaiser, et al., *Stem Cell Fight*, 293 SCIENCE 2369 (2001).

been produced for the purposes of research; and (4) donors must not have been given a financial incentive.[7] The stem cell line derived from the original embryonic stem cell must be viable, show characteristic stem cell morphology, have the ability to be maintained frozen and in culture, and have undergone at least several population doublings.[8]

Sixty-four embryonic stem cell lines met the presidential criteria. The decision restricts federally funded scientists from obtaining human embryonic stem cells from lines other than the 64 existing cell lines that met the presidential criteria. The 64 lines were reported from ten different laboratories in the United States, Australia, India, Israel, and Sweden.[9] The majority of lines were even reported to express all of the markers known to be associated with human embryonic stem cells, including stage specific embryonic antigens, the enzyme alkaline phosphatase, and tumor rejection antigen 1.[10]

To implement the President's decision, the NIH is currently attempting to create a Human Embryonic Stem Cell Registry of the sixty-four existing stem cell lines around the world that meet the eligibility criteria. While basic contact information and data are sought at present, the NIH hopes to expand the registry to include derivation details, the number of passages, culture conditions, and growth characteristics, a description of efforts to characterize the cells, relevant publications, DNA fingerprinting data, and quality assurance data.[11] The Food and Drug Administration also stands ready to work with the scientific community as stem cell research nears the stage of human clinical trials.

Regardless of the federal view regarding embryonic stem cell research, the regulatory problem may remain with the states. Numerous states already govern research on embryos and fetuses and approximately nine states ban human embryo experimentation.[12] This means that even approved stem cell lines or the commercial and therapeutic products resulting from those stem cell lines could be barred from being sold within these states.

The Memorandum Of Understanding (MOU)

To solve some of the technology transfer issues involved in gaining access to HEPSCs, the NIH signed an agreement on September 5, 2001 with the WiCell Research Institute, Inc., of Madison,

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[7] The Fact Sheet released August 9, 2001 from the White House regarding Embryonic Stem Cell Research and the President's address is available at http://www.whitehouse.gov/news.releases/2001/08/print/20010809-1.html; Faith McLellan, *Bush supports limited funding for stem-cell research*, 358 THE LANCET 568 (2001).

[8] Id.

[9] *NIH Update on Existing Human Embryonic Stem Cells*, Aug. 27, 2001, *available at* http://www.nih.gov/news/stemcell/082701list.htm.

[10] Id.

[11] Id.

[12] Sheryl G. Stolberg, *Washington Not Alone in Cell Debate*, N.Y. TIMES, July 23, 2001, at A12.

Wisconsin.[13] WiCell is the group that holds the patents on human embryonic stem cells and the MOU with the NIH makes WiCell's existing five human embryonic stem cell lines more readily available to federally funded researchers.[14] Under the agreement with WiCell, scientists at the NIH have free rein to do basic embryonic stem cell research, though the creation of whole embryos or the use of the cell samples for therapeutic or diagnostic purposes is forbidden.[15] The agreement also enables researchers to be unencumbered by intellectual property disputes as WiCell is forgoing any claim of patent rights to new discoveries that researchers discover during basic research. WiCell retains commercial rights to its materials and will receive a fee to cover handling and distribution expenses in supplying the cell lines. In addition, WiCell agrees within the MOU to allow federally funded non-profit institutions access to the stem cell lines upon the negotiation of similar agreements.

Disadvantages Of The Memorandum Of Understanding

The public should be concerned that their tax dollars are effectively funding the basic research of two private companies without limitation to the potential future royalties of the companies. Of course, the government also retains a royalty-free license to use inventions that result from government funded research, regardless of whether the research was done in an NIH laboratory or a private institution. While such a practice may be common in other scientific industries, military equipment for example, the monopoly on HEPSCs has a much broader potential for future inventions and technologies in many different scientific fields and the results are predicted to have fewer latency problems. The estimated 8 to 12 years until commercial and therapeutic products or uses are realized may enable WiCell to enjoy more of the patent term protection of their monopoly than is usual.

Having legally and fairly granted a monopoly to WiCell through the patent system, the government's MOU basically gave the patentee a blank check by not negotiating potential licensing practices, fees, or royalties upfront. In addition, the President's decision has limited the development of additional embryonic stem cell lines, thereby limiting the threats to Wisconsin's or Geron's domination of the field within the United States. Since WiCell lawfully acquired the patent, WiCell cannot be held liable under the Sherman Act § 2, 15 U.S.C.S. §2, for maintaining the monopoly power they lawfully

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[13] *The Memorandum of Understanding between WiCell Research Institute, Inc. and the Public Health Service*, *supra* note 1.
[14] Id.
[15] *NIH News Release Regarding the NIH and WiCell Stem Cell Research Agreement*, Sept. 5, 2001, *available at* http://www.nih.gov/news/pr/sep2001/od-05.htm.

acquired by refusing to license the patent to others.[16] As long as WiCell and Geron do not try to extend the monopoly to unpatented material, they are basically safe from antitrust liability.[17]

Under the MOU, WiCell has signed away any reach-through rights to discoveries or inventions resulting from basic research. Basically, any researcher who makes a patentable discovery through basic research with WiCell's embryonic stem cell lines will own the patent.[18] But if the researcher wishes to commercialize any discovery made on the basis of WARF's patent, they must negotiate a license with WARF. At present, WiCell currently has 30 Material Transfer Agreement's (MTAs) executed for the human embryonic stem cells and approximately another 100 MTAs in various stages of negotiation with various academic and nonprofit research institutions.[19] In addition, anyone seeking to develop commercial applications of stem cells to the six cell types exclusively licensed to Geron will also have to negotiate with Geron for a sublicense.[20] If an agreement cannot be reached, the patent holder must go directly to WARF, as Geron has no legal right to enforce WARF's patent. In an agreement similar to the MOU between NIH and WiCell, Geron has agreed to allow academic scientists to convert the stem cells into the derivative cell types covered by its agreement with WiCell, but refuses to allow commercialization of the results at this time. Geron has stated that it does not want to impede others from research into the basic biology of stem cells or therapeutic applications but will demand royalties from any commercial products or therapies that are developed.[21] Unlike the MOU between NIH and WiCell, Geron has assured WARF and WiCell that it will sublicense on reasonable commercial terms.[22] As a result, Geron will most likely maximize the number of companies developing commercial products in order to maximize the amount of potential royalties.

No concern is evident within the MOU for the possibility that the patent holder may choose to exercise its rights through licensing or other contractual agreements in a manner inconsistent with the advancement of therapeutic and commercial applications. After allowing the NIH and private federally funded scientists to finish the basic research on WiCell's HEPSC lines, WiCell could potentially block all or selected commercial and therapeutic development and usage through restrictive licensing. At present, there are no written limitations on to whom and on what terms licensing by WiCell and Geron will be

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[16] 35 U.S.C. § 271(d) (1988).
[17] Image Technical Services v. Eastman Kodak Co., 125 F.3d 1195, 1215 (9th Cir. 1997); *cert. denied*, 523 U.S. 1094 (1998).
[18] Nicholas Wade. *Officials say Bush's new stem cell policy may streamline the research process*. N.Y. TIMES, Aug. 18, 2001, at A10.
[19] Bonnie J. Sedlak, *Acquiring Stem Cells for Research: Patenting and licensing issue persist*, GENETIC ENG'G NEWS, Sept. 15, 2001, at 1, 67. A Material Transfer Agreement (MTA) is a contract that codifies the terms of sharing research tools.
[20] Id.
[21] Andrew Pollack, *supra* note 5, at C1.
[22] Bonnie J. Sedlak, *supra* note 19 at 67.

granted. The Government has granted a monopoly, funded it, and apparently failed to consider balances or limitations. It appears that NIH wanted its researchers to have sole access to the HEPSC lines for basic research and a chance to protect the rights of the rest of the HEPSC industry may have been missed. This apparent lack of forethought not only limits competition, but also slows therapeutic and commercial research of stem cells. The only alternative for competitors is to attempt to negotiate with WiCell and Geron or to design around the patents, for example by employing human germ-cell lines derived from aborted fetuses and adult stem cells.

NIH should have negotiated a royalty agreement and/or inserted a fair, reasonable, and nondiscriminatory licensing clause within the MOU to limit, in a reasonable manner, WiCell's monopoly in return for providing WiCell with such a major boost in basic research likely to use WiCell intellectual property. While such clauses may necessitate litigation at a later date, the clauses would effectively limit injunctions against the infringing parties that could stifle competition and retard product development. A deficiency of this approach is that such clauses might only protect the larger and more competitive pharmaceutical companies, but there would be some protection for the competitive market. Although the Government could not and should not force WiCell to forfeit its intellectual property rights, the publicizing of WiCell's unwillingness to allow the reasonable royalty or licensing clauses within the MOU would have essentially forced the company to capitulate. Difficulties with these clauses would be in drafting specific conditions as stem cell research is still in its infancy and neither the breadth of potential products nor their value is clear.

The Government also missed the opportunity to grant and define a strong research exemption to give third parties access to stem cell products and research tools for research purposes without having to obtain permission from the patent holder or to require WiCell and Geron to agree to compulsory licensing under limited and clearly defined circumstances within the MOU. Scientists usually have a research-use exemption that provides protection from patent infringement when the patented invention is used for research purposes only.[23] Then, if a discovery during basic research leads to a commercially valuable invention, WiCell could still exclude the discoverer from making, using, and selling the invention.[24] This research exemption would just make the access to WiCell's stem cell lines a bit less complicated.

Under the MOU, WiCell allows third-party stem cell lines to be used for basic research with immunity from infringement injunctions but with the restriction that the third party may not directly or indirectly retain rights to their materials.[25] In addition, laboratories that utilize both WiCell and third-

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[23] Id. at 54
[24] Id.
[25] *The Memorandum of Understanding between WiCell Research Institute, Inc. and the Public Health Service*, *supra* note 1.

party lines may only use the HEPSC lines for teaching or non-commercial research purposes.[26] This excludes sponsored research where the sponsor receives a right to the results of the sponsored research. This requirement of the MOU basically limits labs to federal funding and WiCell lines. If the labs want to use third party lines with private funding, they run the risk of an infringement suit by WiCell. If they want to use WiCell lines, they cannot have private funding and are limited to federal funding resources. Basically, WiCell has a win-win situation to continue its U.S. domination of the stem cell research field.

The NIH could have also negotiated a broader covenant not to sue from WiCell. This is important, as international laboratories are afraid to make or sell their stem cell lines in the United States for fear of an infringement suit from WiCell. These companies must obtain a license from WARF if the cells match the WARF's patent description. While WiCell cannot sue international laboratories that 'give' portions of their cell lines to federally funded American researchers, WiCell can sue the American researchers who take the international cell lines for infringement under WiCell's patent monopoly. WiCell can obtain an injunction against anyone who makes, sells, or uses an infringing stem cell line. This patent monopoly gains WiCell almost an exclusive hold on all federally funded embryonic stem cell research within the legal boundaries of the United States. In the alternative, WiCell can allow the government to fund the research on the international cell lines, get the information, and then sue for infringement before or when a commercial or therapeutic use is developed. By reserving the right to sue until after the basic research is accomplished, WiCell could potentially force excessive license fees upon the inventive party.

Still, the cell lines within international borders are not limited by President Bush's decision or WARF's patent monopoly within the United States. Because of this and as a result of the adoption of more liberal policies regarding the use of human embryonic stem cells in other countries, the United States is losing talented researchers who want to continue their research in a more receptive environment.[27] While WARF and Geron have both filed for numerous international patents, all of the patent filing requests are still within the application phase at present and pose no immediate danger of infringement suits.[28]

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[26] Id.

[27] 147 CONG. REC. H.5327, 5329 (daily ed. Aug. 2, 2001) (statement of Mr. McDermott) (speaking on embryonic stem cell research and the advantages of public funding).

[28] Geron filed WO 99/20740 A2 "Methods and Materials for the Growth of Primate-Derived Primordial Stem Cells"; Geron filed WO 99/20741 A1 "Methods and Materials for the Growth of Primate-Derived Primordial Stem Cells"; WARF filed WO 00/12682 A1 "Primate Embryonic Stem Cells With Compatible Histocompatibility Genes"; WARF filed WO 01/34776 A1 "Hematopoietic Differentiation of Human Embryonic Stem Cells"; Geron filed WO 01/51616 A2 "Techniques for Growth and Differentiation of Human Pluripotent Stem Cells"; WARF filed WO 01/62899 A2 "Method of Making Embryoid Bodies from Primate Embryonic Stem Cells"; WARF also filed WO 01/66697 A2 "Serum Free Cultivation of Primate Embryonic Stem Cells."

Benefits Of The Memorandum Of Understanding

The most important benefit of the MOU is that it enables researchers to gain access to WiCell's stem cell lines for basic research. Despite the block on therapeutic and commercial research by the MOU, the estimated gain of information from the federally funded basic research retains an enormous potential. From the basic research, scientists hope to create a fundamental base of knowledge about how the stem cells function and how to manipulate them. Examples include determining the best conditions for growing the cells, directing the differentiation of the stem cells into specialized cells, and learning about key genes that control proliferation of the stem cells in an undifferentiated state.

The second most important benefit of the MOU is that it enables researchers to gain access to stem cell lines that qualify for federal funding under the President's criteria. Government assistance in the form of federal funding is necessary in order to ensure equal access to the qualified stem cell lines, to promote investment in this promising line of research, to encourage sound public policy, and to foster public confidence in the conduct of such research.[29] In addition to being the most efficient way to further basic embryonic stem cell research, federal funding is the only realistic source for the large and sustained infusion of funds that is necessary for the research. President Bush's federal funding plan, now enabled by the MOU, may also provide motivation for the private sector to get involved and transform the basic research into disease therapies.[30]

A third benefit of the MOU is that it will expedite the research on stem cells. The MOU enables multiple parties to pursue simultaneously this critical research, and thereby increases the chances for significant discoveries over a shorter period of time. The MOU also provides a comprehensive ethical oversight to the stem cell research. Private organizations and overseas researchers will still have stem cell research, but without the comprehensive ethical oversight provided by U.S. human subjects regulations.[31]

The potential benefits to the public may be greater than the risk of financing a private and legal monopoly. Right now, the NIH has satisfied its goal as a basic research institution to gain its scientists access to the research tools. Only the future will tell us whether the lack of limitations on the patent holder was worth the gain.

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[29] Audrey R. Chapman, et al., *Stem Cell Research and Applications Monitoring the Frontiers of Biomedical Research* (The Am. Assoc. for the Advancement of Sci. and Inst. for Civil Soc'y), Nov. 1999, at vi.

[30] The testimony of Tommy G. Thompson, Secretary of Health and Human Services given at the Senate, Health, Education, Labor and Pensions Committee, in Washington, D.C. on Sept. 5, 2001 on Embryonic Stem Cell Research is available at http://www.hhs.gov/new/speech/2001/010905.html.

[31] Robert P. Lanza, et al. *The Ethical Reasons for Stem Cell Research*, SCI. MAG., May 18, 2001, at 1299.

Conclusion

Many scientists believe that human embryonic stem cell research holds incredible promise over time because of the capacity of embryonic stem cells to develop into any tissue in the human body. The NIH's MOU with WiCell has enabled federally funded researchers to gain access to WiCell's HEPSC lines for basic research. While there seems to be an egregious lack of foresight in limiting WiCell's legal monopoly over HEPSC development in return for the federal funding boost to basic research involving WiCell's patents, the basic research that has been expedited may lead to creating therapies for diseases like Parkinson's and Alzheimer's, or even to evaluate the safety and efficacy of new medicines from an increased understanding of basic biology.

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