



# Stem Cell Patents- Reexamination/ Litigation – The Last Five Years

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## ABSTRACT

U.S. patents directed to stem cell technologies have generated a high degree of interest as well as controversy. Many patents relating to stem cell technology have either faced reexamination and/or litigation.

The United States Patent and Trademark Office (USPTO) recently upheld three Wisconsin Alumni Research Foundation (WARF) stem cell patents following reexamination requested by a third party challenger in 2006. StemCells, Inc. and Neuralstem, Inc. both filed suits with respect to their patents related to neural stem cells. StemCells filed a suit on July 24, 2006, alleging infringement of its patents collectively referred to as “the neural stem cell patents”, by Neuralstem, Inc. Neuralstem, Inc., filed a suit against StemCells, Inc. on May 7, 2008, alleging inequitable conduct during prosecution of StemCells’ U.S. Pat No. 7,361,505. Both suits are yet to be decided. Pharmastem Therapeutics, Inc. had attempted to enforce its U.S. Patent Nos. 5,192,553 and 5,004,681, which resulted in invalidation of the patents in 2007. It remains to be seen what effect (if any), the recent increases in funding of stem research and the important U.S. Supreme Court decision on *KSR v. Teleflex, Inc.* (making it more difficult to establish non-obviousness of patentable subject matter), will have on challenges to stem cell patents.

## INTRODUCTION

Stem cells are undifferentiated cells which can give rise to a succession of mature functional cells. The patenting of stem cells (especially embryonic stem cells) has created much controversy and interest in the United States, and in the international scientific and intellectual property (“IP”) communities. The controversy, at least with respect to research in human embryonic stem cells emanates from techniques used in the creation and usage of stem cells, that require the destruction of a human embryo. Embryonic stem (ES) cells are derived from totipotent cells of the early mammalian embryo and are capable of unlimited undifferentiated proliferation *in vitro*. They were first derived from mouse embryos<sup>1,2</sup>. A breakthrough in human embryonic stem cell research came in November 1998, when a group led by James Thomson at the University of Wisconsin-Madison first developed a technique to isolate and grow the cells when derived from human blastocysts<sup>3</sup>. The huge interest in embryonic stem cells lies in the apparently unlimited therapeutic possibilities presented by their pluripotency and self renewal.

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## SOME RECENT CHALLENGES OF STEM CELL RELATED PATENTS

There have been several challenges to patents related to stem cells in the U.S., with The Wisconsin Alumni Research Foundation (WARF), Neuralstem, Inc., Phamastem Therapeutics, Inc., and StemCells, Inc. most frequently making the news headlines.

### **The Wisconsin Alumni Research Foundation**

**(WARF):** WARF is the nonprofit technology transfer office of the University of Wisconsin (UW)-Madison, which patents the discoveries of UW-Madison researchers and licenses these technologies<sup>4</sup>.

Between 1998 and 2006, the University of Wisconsin was awarded three U.S. patents: U.S. Patent Nos. 5,843,780; 6,200,806; and 7,029,913. Prior to amendment of the claims following reexamination, these patents together covered the entirety of all stem cells, no matter how the cells were derived. These patents are licensed to about 15 companies and 365 academic groups. The foundation manages more than 940 active license agreements with companies around the world. Over \$1 billion (2004 income) of products are sold each year under license from WARF.

Two parties, the Public Patent Foundation (PUBPAT) and the Foundation for Taxpayer and Consumer Rights (FTCR) (now Consumer Watchdog), asked the U.S. Patent and Trademark Office (USPTO) to reexamine the patentability of the WARF patents in September of 2006. In response to rejections made by the Examiner during reexamination, claims 1-3 in U.S. Patent No. 7,029,913 (the '913 patent) were amended, limiting the claims to cells derived from a pre-implantation embryo. The claims as amended in a Supplemental Response filed on October 4, 2007, define a replicating in vitro culture of pluripotent human embryonic stem cells derived from a pre-implantation embryo wherein the cells (i) will proliferate in an in vitro culture for over one year in an undifferentiated state without the application of exogenous leukemia inhibitory factor, (ii) maintain a karyotype in which chromosomes are euploid through prolonged culture, (iii) maintain the po-

tential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) are inhibited from differentiation when cultured on a fibroblast feeder layer. The USPTO found the amended claims allowable on February 25, 2008, closing prosecution on the merits. The claims in U.S. Patent Nos. 5,843,780 and 6,200,806, were similarly limited during reexamination to cells derived from a preimplantation embryo and then allowed by the USPTO. The third party requester, Consumer Watchdog filed an Appeal Brief in connection with the reexamination of U.S. Patent No. 7,029,913 on September 18, 2008, appealing from the finding of patentability of claims 1-3, made by the Examiner, alleging that the U.S. Patent Office made two critical errors that led to the allowance of the amended claims. They argued that (i) the standard for obviousness in view of the prior art was not whether the prior art made the claimed subject matter obvious with absolute certainty and (ii) the Examiner's conclusion, that since human embryonic stem cell cultures as claimed had not existed before the patent application was filed they could not have been obvious over the prior art effectively eviscerates the non-obviousness requirement by making it the same as anticipation, a standard which is too high for challengers to meet, and conflicts with binding precedent. In summary, the challenger asserts that the Patent Office used too easy a standard of patentability, and the patents should have been revoked. The two third party groups ascribe the announcement by WARF to substantially ease its licensing agreements (discussed below) to the patent challenge.

**Neuralstem, Inc. v. StemCells, Inc.:** In a different proceeding, StemCells, Inc. (StemCells) filed a suit against Neuralstem, Inc. (Neuralstem) on July, 24, 2006, alleging infringement of U.S. Patent Nos. 5,851,832, 6,103,530, 6,497,872, and 6,294,346 (collectively, "the neural stem cell patents") assigned to or exclusively licensed to StemCells<sup>5</sup>. StemCells amended the complaint on July, 7, 2006 to include U.S. Patent No. 7,101,709. Neuralstem then filed requests for reexamination of "the neural stem cell patents" on December 7, 2006, and April

5, 2007. As a result of the reexaminations, on June 19, 2007, StemCells and Neuralstem jointly agreed to stay the lawsuit. In a related proceeding, Neuralstem filed a suit against StemCells on May 7, 2008, requesting declaratory judgment of unenforceability, invalidity and non-infringement of U.S. Patent No. 7,361,505 (the '505 patent) one of "the neural stem cells patents" exclusively licensed to StemCells. Neuralstem alleged that StemCells had withheld information material to the patentability of the '505 patent- i.e., the pending litigation with Neuralstem, the re-examination of "the neural stem cell patents", the prior art cited therein, the adverse office actions issued during reexamination as well as amendments made to the claims to overcome the rejections<sup>6</sup>.

In May of 2008, Neuralstem filed a motion to reopen the infringement lawsuit with StemCells, being heard in the United States District Court for the District of Maryland Southern Division<sup>5</sup>. A decision is pending in both cases.

In other developments, the European Patent Office in June 2007 granted to Neuralstem European Patent EP0915968, covering the "Isolation, Propagation and Directed Differentiation of Stem Cells from Embryonic and Adult Central Nervous System of Mammals." The claims in EP 0915968 define a method for expansion and culture in vitro (claims 1, and 4-6)/a method of differentiation of an in vitro culture (claims 3-6 and 11-12), of stem cells of the central nervous system of a mammal, wherein the stem cells maintain the multipotential capacity to differentiate into neurons, astrocytes and oligodendrocytes, and, an in vitro adhesion culture of stem cells of the central obtained by the claimed method of expansion and culture in vitro, of stem cells (claim 2 and 9-10). Related Patent Nos. 5,753,506 and 6,040,180 were granted in the U.S. The European patent has now been validated in several European countries including France, Germany, Ireland, Spain, Sweden, Switzerland and the United Kingdom. Neuralstem's technology allows for the production of commercial quantities of neural stem cells isolated from the human brain

and spinal cord, and for the differentiation of such cells into mature, physiologically relevant human neurons and glia. StemCells filed a Notice of Opposition to the European patent on April 21, 2008. An invitation to file Observations to the Notice of Opposition was mailed to the Applicant, Neuralstem on May 5, 2008. A response by Neuralstem is pending following their request for an extension of time for filing a response, which was granted by the European Patent Office on October 21, 2008.

**Pharmastem Therapeutics, Inc.:** Pharmastem Therapeutics, Inc. has alleged patent infringement on several occasions against multiple companies, for U.S. Patent Nos. 5,004,681 (the '681 patent) and 5,192,553 (the '553 patent). The patents cover methods for the collection, preservation and culture of umbilical cord and placental blood. These alleged infringements have included a case brought before several courts, the first appearance occurring on February 22, 2002, when Pharmastem filed a lawsuit against eight private cord blood banking companies: ViaCell, Cryo-Cell, CorCell, Cord Blood Registry, StemCyte, NuStem, Bio-Cell, and Birthcells. At the conclusion of the original trial, the jury returned a verdict in favor of Pharmastem, Inc. finding both patents valid, enforceable and willfully infringed. The U.S. District Court for the District of Delaware, in response to the defendants' motions for Judgment as a Matter of Law (JMOL), reversed the jury verdict, entering JMOL of non-infringement with respect to both patents<sup>7</sup>. The District Court concluded that Pharmastem had failed to provide proper evidence proving a critical requirement of its patents, US Patent Nos. 5,192,553 and 5,004,681. The two patents covered compositions containing stem cells "in an amount sufficient to effect hematopoietic reconstitution of a human adult", therefore, to prove infringement, Pharmastem had to show that the blood defendants collected had a sufficient supply of stem cells to meet this purpose. The District Court did confirm the validity of the patents, however. Pharmastem appealed from the JMOL orders of non-infringement to the Federal Court of Appeals for the Federal Circuit. In the infringement action brought against the de-

defendants, PharmaStem asserted claims 1 and 2 of the '681 patent, as amended in reexamination, and claims 13, 19, 47, 53, and 57 of the '553 patent. On July 9, 2007, the Federal Court of Appeals affirmed the District Courts judgment as to the infringement issues. The Federal Court of Appeals then directed entry of judgment for the defendants with respect to the counterclaim of invalidity for obviousness, thus reversing the judgment of the District Court<sup>8</sup>. A Petition for writ of certiorari to the U.S. Supreme Court was denied on March 17, 2008<sup>9</sup>.

## **ADVANCES IN STEM CELL RESEARCH; CHANGES IN FUNDING AND STATE LAWS**

Great strides have been made in the area of stem cell research funding in the U.S. since 1995, when the U.S. Congress enacted into law an appropriations bill which prohibited federally appropriated funds from being used for research where human embryos would be either created or destroyed. This has not stopped stem cell research. The California Institute for Regenerative Medicine ("The Institute" or "CIRM") was established in early 2005. As of August 2008, CIRM had approved grants totaling over \$600 million and has committed about \$1 billion through June, 2009, making it the worlds largest funder of embryonic stem cell research<sup>10</sup>. The State of Missouri passed Amendment 2 in November, 2006, which allows usage of any stem cell research and therapy allowed under federal law, but prohibits human reproductive cloning<sup>11</sup>. Eight other states in the U.S. committed funding for stem cell research that total under \$2 billion<sup>12</sup>.

WARF announced in 2007 that Industry-sponsored stem cell research will be facilitated by a new WARF policy enabling companies to sponsor research at an academic or non-profit institution without a license, regardless of location and regardless of intellectual property rights passing from the research institution to the company. This should enable companies to conduct stem cell research in a low-cost, visible manner, and increase funding of stem cell research by for-profit companies.

As of 2008, it is clear that public attitude towards funding for embryonic stem cell research has undergone a dramatic change since 1995. A recent discovery by scientists at the Univerisity of California and Wake Forest University School of Medicine that human embryonic stem cells can be obtained without embryo destruction<sup>13</sup> could revolutionarize stem cell research and remove or reduce the moral roadblocks to funding. In a similar vein, the discovery by separate research groups in late November of 2007, that human stem cells can be made from adult skin, without using embryos or eggs was termed "A Stem Cell Victory" by the U.S. News and World Report<sup>14</sup>. The two groups are headed by Shinya Yamanaka of Kyoto University and James Thomson of the University of Wisconsin. These cells, known as induced pluripotent stem cells (iPs), have a normal karyotype, express the cell surface markers and genes that characterize human embryonic stem cells, and maintain the developmental potential to differentiate into derivatives of all primary germ layers<sup>15</sup>. Kyoto University in Japan acquired the the world's first patent (Japanese Patent No. 2008-131577), for iPS cells in September, 2008.

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## CONCLUSION

The increased funding/potential reduction in research cost (WARF announcement) could have a two prong effect- it could hasten the development of U.S. stem cell technology, and/or it could increase the amount of litigation of stem cell patents especially since current opinion is that is more difficult to get a valid patent, and easier to challenge existing patents as obvious over the prior art in view of the recent Supreme Court decision in *KSR Int'l Co. v. Teleflex*<sup>16</sup>.

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