

Challenges to Stem Cell Patents in Europe and the U.S.

By A. Antony Pfeffer and John Murray

Recently, scientists have announced the discovery of how to convert human skin cells into stem cells. Gina Kolata, *Man Who Helped Start Stem Cell War May End It*, N.Y. TIMES, Nov. 22, 2007, at A1. Stem cells are cells with the nascent ability to grow into fully formed organisms. Certain types of human stem cells have the potential to grow into individual human beings, which has resulted in a great deal of controversy surrounding stem cell research. Many individuals, as well as certain organizations, particularly religious organizations, see human stem cell research as a fundamental challenge to human dignity and the sanctity of life. This debate has affected patent law in Europe, to the extent that inventions based on certain kinds of research may be excluded from patentability. However, new methods of stem cell research, such as the recent conversion of skin cells into stem cells, may escape the ethical barriers that currently exist in European patent law. In addition to their potential ability to sidestep the ethical barriers to patenting stem cells, these new research approaches can open new scope for researchers to perform stem cell research in the United States.

EUROPEAN ETHICAL REGULATIONS

At this time, in Europe, researchers are restricted in their ability to obtain patents on their research because of ethical regulations that bar the patenting of the “human embryo.” Under Rule 23d(c) of the European Patent Convention, the patenting of biotechnological inventions is prohibited for uses of human embryos for industrial or commercial purposes. This regulation derives from Article 53(a) of the European Patent Convention, which prohibits patenting inventions contrary to morality or “ordre public.” The European Patent Office (“EPO”) has taken a broad interpretation of this prohibition, and thus has excluded from patentability both patents that cover processes of extracting human stem cells from human blastocysts and patents covering human embryonic stem cell lines.

The EPO has rejected claims on human embryonic stem cells as unpatentable, for example those of EP0770125 owned by the Wisconsin Alumni Research Foundation (“WARF”). A technical Board of Appeal has issued an interlocutory decision (Case No.: T 1374/04), referring the question to the Enlarged Board of Appeal, whose decision is now pending. The questions posed to the Enlarged Board of Appeal ask it to define the relationship between the morality clauses within European patent law and stem cell research. While the decision remains pending, the EPO has suspended the examination of human embryonic stem cell-related applications. Consequently, researchers or organizations seeking to patent human embryonic stem cell-related inventions in Europe should ensure they remain informed of developments in the pending WARF case appeal. Even if the appeal ultimately results in the broad exclusion of human embryonic stem cells from patentability, it may remain the case that individual countries, such as the UK, will still grant patent protection.

THE THOMSON PATENTS

In the United States, the U.S. equivalents to EP0770125 (US Pat. No. 5,843,780, US Pat. No. 6,200,806 and US Pat. No. 7,029,913 (“the Thomson patents”)) were allowed, as the United States has no similar restriction. These patents form, according to some commentators, a very significant group of patents on human embryonic stem cells. The Thomson patents, which issued between 1998 and 2006, broadly claim primate embryonic stem cells, human embryonic stem cells, and cultures of human or primate embryonic stem cells respectively. WARF licenses its patent rights through its subsidiary WiCell. WARF has claimed it has provided cells to more than 400 research groups in 40 states and 24 countries, and that it has 18 commercial licensees with companies that are developing various research products, diagnostics, and therapies.

In addition to those patent rights held by WARF, the Geron Corporation (“Geron”) holds a license to the exclusive commercialization rights for three significant cell types: neural, cardiomyocytes (heart muscle tissue), and pancreatic islet (insulin-producing) cells made from embryonic stem cells for therapeutic and diagnostic products. Pursuant to Geron’s agreement with WARF, Geron may transfer the undifferentiated cell lines only to Geron collaborators for work on projects described and directed by Geron. Consequently, researchers seeking to use stem cells within these specific research fields may need to contact Geron before proceeding, or they could risk a suit for infringement of the patent rights.

Some commentators consider the Thomson patents to be a barrier to stem cell research in the United States due to the breadth of their claims. However, recently WARF announced a relaxation in its licensing policy for these patents (*see*

www.wicell.org or <http://stemcells.nih.gov/research/registry> for documents reflecting WARF policies). WARF stated that it will enable 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. WARF claims this will enable companies to get started with stem cell research in a low-cost, visible manner and increase funding of stem cell research by for-profit companies. But companies will still need a license when they want to bring such research into their company laboratories or when they want to develop a product for the market.

The claims of the Thomson patents are directed toward the processes of manufacture for stem cells and cell lines, and the compositions of the stem cells, and cell lines *per se*. They claim purified preparations of pluripotent primate and human embryonic stem cells (meaning cells that can form specialized body tissues, but cannot develop into a full human being), and replicating *in vitro* human embryonic stem cell cultures that have four specific characteristics: the cells can 1) proliferate in an *in vitro* culture for over one year; 2) maintain a normal and stable number of chromosomes (the karyotype) without noticeable alteration through prolonged culture; 3) have the potential to differentiate into the three germ layers (the

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different collections of cells which will develop into tissues and organs), endoderm, mesoderm and ectoderm, throughout the culture; and 4) will not differentiate when cultured on a fibroblast feeder layer (a layer of cells that assists stem cell growth in culture by feeding them). Any pluripotent human embryonic stem cells with these four characteristics may potentially fall within the scope of the Thomson patent claims.

The Thomson process claims (in US Pat No. 5,843,780 and US Pat. No. 6,200,806) describe the isolation of pluripotent primate or human embryonic stem cell lines by 1) isolating a human blastocyst (blastocysts are cell structures formed in early embryogenesis); 2) isolating cells from the inner cell mass ("ICM") of that blastocyst; 3) plating the ICM cells on embryonic fibroblasts, where a mass of cells derived from the ICM cells can grow; 4) dissociating the grown cell mass into dissociated cells; 5) replating the dissociated cells on embryonic feeder cells; 6) selecting colonies with compact morphologies and cells with high nucleus-to-cytoplasm ratios and prominent nucleoli; and 7) culturing the cells of the selected colonies to obtain an isolated pluripotent stem cell line. The Thomson patents claim any human or primate pluripotent stem cell lines isolated by this process regardless of whether such stem cell lines are within the composition claims. Reportedly, WARF claims its patents apply to all human embryonic stem cells inside the United States.

The '780 and '806 patents are undergoing re-examination under *ex parte* re-examination proceedings (under Serial Nos. 90/008102 and 90/008139, respectively), while the '913 patent is being re-examined *inter partes* (under Serial No.

95/000154). Recently, in all three re-examinations, the U.S. Patent and Trademark Office rejected all claims of the Thomson patents. However, the eventual outcome of the re-examinations may be only minor modifications to the scope of the patents. Even if the U.S. Patent and Trademark Office ultimately invalidates the patents, it is extremely likely that an appeal through the federal courts would be mounted. Therefore, for the foreseeable future, any researchers wishing to employ human embryonic stem cells within the United States may have to consider licensing the Thomson patents.

HOPE FOR RESEARCHERS

However, there is hope for researchers wishing both to seek patent protection in Europe, and who wish to avoid issues with licensing the Thomson patents. Researchers, including Dr. Thomson, have recently announced that normal human skin cells may be reprogrammed to an embryonic state. This raises the possibility that the objections to patentability raised by morality clauses in Europe (or elsewhere) may be eliminated. As this new technology would not be making use of embryonic stem cells, the Thomson patents, directed to embryonic stem cells, would be avoided. One result of the research efforts that have been made in new directions for stem cell research is that academic and commercial entities will have a significantly increased likelihood of establishing patentable inventions clear of third-party patent claims or regulatory concerns in both the United States and Europe.



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