Consternation and Confusion following EU Patent Judgment

Cell Stem Cell
Letters

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DOI 10.1016/j.stem.2011.11.002

The Court of Justice of the European Union recently issued a judgment that it is not acceptable under European law to patent techniques for derivation of other cell types from hESC lines. This decision was a great disappointment for many stem cell researchers and to the patient groups who hope one day to be treated with stem cell derivatives. As is to be expected in law, there is a remorseless logic to this opinion given that the role of the Court is to apply the rules established by Parliament. However, there is confusion in that the same European Union that established these rules also provides funding for research with hESCs as do the parliaments of several member states. In other words, one arm of the EU is branding as immoral a research activity that is being encouraged by another.

The basis of the case rests deep within a series of treaties and agreements whose purpose is to create a common market for the members of what is now the European Union. The first of these was the Treaty of Rome in 1957. Procedures for patenting and limitations as to what may be the subject of a patent have been described in great detail since then.

Specifically, the judgment has its origin in Directive 98/44 from the European parliament and the Commission in 1998. In Article 6 Paragraph 1 of that agreement it is stated that:

> Inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.
>
> Paragraph 2
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> On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:
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> (c) uses of human embryos for industrial or commercial purposes;…

The case was brought by Professor Oliver Brüstle, who is Professor of Reconstructive Neurobiology at the University of Bonn and Co-Founder and Scientific Director of LIFE & BRAIN GmbH. He and his colleagues have a distinguished reputation for their innovative research in neurobiology. In December 1997 they filed a patent describing a novel method for the isolation of neural stem progenitor cells from hESCs with the expectation that they might form the basis of treatments for neurodegenerative diseases such as Parkinson's disease. Greenpeace were successful in obtaining a judgment from the Federal Patent court of Germany that aspects of the patent relating to hESCs were invalid because it involved use of hESCs. The Federal Court of Justice decided to refer an appeal made by Oliver Brüstle to the European Court because the meaning of the term "embryo" had not been defined in Directive 98/44. It was the final judgment of this appeal that was published in October. As summarized in the Press Release, the Court found that, "A process which involves removal of a stem cell from a human embryo at the blastocyst stage, entailing the destruction of that embryo, cannot be patented." In the case of this patent it cannot ever be reinstated. Only a change in the directives from the EU could lead to a different judgment on a new application on a similar invention.

This judgment contrasts starkly with the fact that the EU in successive Framework funding packages has supported research with hESCs. Several member countries including Finland, Greece, the Netherlands, Sweden, and the UK allow the production of hESC lines from surplus IVF embryos. Indeed, in Germany the 2002 Stem Cell Act, revised in 2008, allows the import of hESCs for specific, approved research objectives. The hESC lines must have been derived before May 1, 2007 from surplus embryos produced by in vitro fertilization. Imposition of this deadline was considered to ensure that no hESC lines are produced specifically for the research in Germany.

Many scientists and others have expressed the view that this judgment will delay the introduction of new therapies to the disadvantage of patients. If researchers are unable to patent their inventions, they may find it more difficult to obtain funding for research with hESCs in Europe, in particular for the translational phase of the development of new therapies. This very expensive phase of research is often funded by companies who are persuaded that the product has real potential. They may invest either alone or in partnership with government agencies, and they expect to protect their investment by patenting the new procedures. Of course it is possible to seek patent protection in other parts of the world, such as the USA and Asia, but competing companies would be able to use the method in Europe with no fear of infringement.

Some commentators have argued that the intention to apply for a patent leads to greater secrecy in early phases of the research, and that by contrast, sequencing of the human genome was accelerated by openness between laboratories. However, in the case of a genome, the novelty required to justify a patent comes from development of new uses of the sequence for a stated purpose rather than a description of the gene. It is hard to believe that companies will invest heavily in new techniques for differentiation of hESCs and then release them for use by everyone. Furthermore, secrecy is not a realistic alternative. Detailed protocols for the

production of cells that are to be used clinically will have to be provided when organizations seek regulatory approval. By contrast, patents provide transparency and thus facilitate competition and progress.

The judgment refers only to ESCs, and a great deal of research is being carried out with other types of stem cells. A stated objective of Greenpeace UK is to bring pressure to increase research with alternatives to hESCs. There is no doubt that researchers do consider alternatives and that great interest is placed upon iPSCs. Patent applications made in the future can encompass both sources of pluripotent cells, but iPSCs are a relatively new invention, so early applications such as that made by Oliver Brüstle did not. It would be wasteful and it would delay treatment of patients if existing protocols for use of hESC derivatives are not taken to the clinic because the procedure cannot be patented.

Finally, there is a real concern that Europe will be perceived as reactionary and resistant to progress in light of this regulation and that as a result, companies will choose to invest in other regions of the world. It is certainly to be hoped that this is not the case, because Europe has a fine record of research with both embryonic and tissue stem cells.

European Court Ruling on Embryonic Stem Cells: Ripple Effects

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DOI 10.1016/j.stem.2011.11.001

The recent Court of Justice of the European Union (2011) opinion in Brüstle v. Greenpeace caught the attention of the California Institute for Regenerative Medicine (CIRM) and many others as a result of its severe restriction on the patentability of inventions arising from embryonic-stem-cell-related research. Strong criticism of the decision immediately arose in some quarters, including dire predictions that the ruling marked the end of human embryonic stem cell (hESC) research in Europe and, ultimately, that Europe would not have access to resulting therapies (Naik, 2011). At CIRM we fund academic and commercial scientists conducting stem cell research ranging from basic science through to early clinical work, and a significant proportion of our funded projects involve hESCs. We appreciate that patent protection can be an important incentive for investment, and that it also often promotes innovation as it allows innovators time and a mechanism to recoup their outlay (Rai et al., 2010). Our view is that the impact of the recent Court ruling on stem cell research and regenerative medicine will be significant but varied. In some instances, the ruling may deter European hESC research, in others such research may nonetheless continue or even increase; in still others, no impact may occur.

In the area of basic or foundational hESC research, for example, we would not expect a significant impact from the Court ruling provided scientists expect that there will be continued funding of such research by government and not-for-profit entities. We would not expect that a diminished ability to obtain patent protection for basic research inventions would materially decrease research funding from these sources. Government funders tend to be less profit-driven than commercial funders. Moreover, hESCs presently remain the "gold standard" for regenerative medicine research (Smith et al., 2009; Fung and Kerridge, 2011). We believe scientists conducting basic research will be reluctant to focus exclusively on adult stem cells or even induced pluripotent stem cells (iPSCs) given the unique advantages offered by hESCs.

With respect to translational hESC research, the situation is more complicated. At this stage of research and development, profit-driven biotechnology and pharmaceutical companies are more actively involved. To the extent that the lack of patent protection following the Court ruling decreases the profit available (e.g., because patented inventions cannot be licensed and injunctions cannot be obtained to protect hESC patented inventions), biotechnology and pharmaceutical companies may be less motivated to invest in European hESC research. That effect may be even more dramatic for startup companies. A strong patent portfolio traditionally has been a prerequisite for attracting venture capital in the life sciences field. As reported by a U.S Department of Commerce white paper, "In a large-scale survey conducted in 2008, 76% of startup managers reported that VC investors consider patents important to funding decisions." (Rai et al., 2010.)

On the other hand, we would not predict a complete dearth of European commercial investment in the hESC sector in the EU for several reasons. First, companies can still protect some of their work as traditional trade secrets. Second, as is often said of biologics, "The product is the process." EU regulators will likely require that any company wishing to compete would have to incur the large expense of preclinical and clinical trials using their particular stem-cell-based therapy (Tam, 2010). Third, to varying degrees throughout Europe, the "Bolar Exemption" (European Union, 2004) limited patent protection for certain types of research at this phase even before the Court ruling. Finally, the effect of the