Today, the position of the European Patent Office (EPO) as to the patentability of human embryonic stem cells (hESCs) is clear. A European patent can only protect an invention involving such cells if, at the “relevant date”, the cells could be obtained by means other than the destruction of a human embryo. In practice, the EPO no longer raises any objection under Article 53(a)EPC in conjunction with Rule 28(c)EPC against applications filed after 10 January 2008. Below we will take a close look at the criteria currently applied by the EPO to decide on the patentability of such inventions.

Concurrently, companies producing and/or marketing hESCs are concerned about what will become of their applications (and patents) in the United States. In effect, according to the recent Guidelines issued by the United States Patent and Trademark Office (USPTO), the American Examiners refuse to examine the patentability of cells that are not “significantly different” from naturally occurring cells (such cells would not be “eligible” for patent protection).

A. Human embryonic stem cell patentability in Europe

A.1. Further to the Brüstle C-34/10 decision by the European Court of Justice (ECJ, 18 October 2011), the European Patent Office amended section G-II, 5.3. of the Guidelines relating to examination of European applications concerning the patentability of inventions using human embryos.
Therefore, the new Guidelines, published in June 2012, imposed that inventions involving "a product which at the filing date of the application could be exclusively obtained by a method which necessarily involved the destruction of human embryos from which the said product is derived" be excluded from patentability, "even if the said method is not part of the claim" and this, regardless of when destruction occurred.

Thereafter, the position of the EPO examiners toughened. If at any point in the invention development process it was necessary to destroy an embryo, the application was rejected in accordance with Article 53(a)EPC in conjunction with Rule 28(c) EPC. In particular, inventions using (or obtained by) commercially available pre-established hESC lines were systematically rejected. The examiners considered that it was not possible to generate hESC lines without destroying an embryo.

On this subject, by decision T 2221/10, published on 4 February 2014, an EPO Board of Appeal decided that the use of commercially available hESC lines is not sufficient to meet the requirements of Article 53(a)EPC if, at the "relevant date" (see below), these cell lines could only be obtained by destroying an embryo.

This represented considerable toughening of the EPO's position since, between 2008 and 2012, the EPO granted patents for inventions involving such cell lines, as their use did not momentarily require involvement of a human embryo (G2/06).

A.2. To establish whether cells are obtained by the destructive use of a human embryo, it is necessary, again according to the Guidelines published in 2012, to take into consideration not only the teaching of the application, but also "the state of the technique at the filing date".

To this effect, development of a new technology for obtaining hESC lines without destroying an embryo rendered such practices more flexible.

This technology was developed by the team of Chung et al. (Chung et al, Human Embryonic Stem Cell lines generated without embryo destruction, Cell Stem Cell (2008)). Today, the EPO's examiners consider that this work is pioneering in this field. Consequently, they assume that, until 10 January 2008 (date of publication by Chung et al.), there was no means for the person skilled in the art to obtain hESCs not having required destruction of a human embryo.
Consequently, any patent applications filed before 10 January 2008 are today rejected on the basis of Art.53(a) and R.28(c)EPC if they involve hESCs.

By contrast, a European patent involving hESCs could be issued if its date of filing is after 10 January 2008. In effect, the EPO’s examiners consider that, in this case, the person skilled in the art was able to reproduce the invention without destroying a human embryo, by using, for example, the technology by Chung et al. The invention, as disclosed in the application, must not necessarily have been obtained with cells generated according to non-destructive embryo technology. However, the applicant must be able to demonstrate that the invention can be reproduced, at the date of filing, using such cells (if the examiner has a doubt, an objection will be raised, even if the application was filed after 10 January 2008). This demonstration must not however necessarily feature in the description of the application.

If such an objection is raised in accordance with Article 53(a)EPC or Rule 28(c) EPC, it is not possible to resolve it by adding a disclaimer excluding the destructive use of a human embryo. As a matter of fact, by decision T1441/13, published on 9 September 2014, an EPO Appeal Board considered that such a disclaimer is unacceptable if, at the "relevant" date of the application (see below), all known methods for producing hESCs were embryo-destructive. In this case, "the remaining subject-matter" after introduction of the disclaimer is not implementable at the date of the application and is considered as insufficiently described (which is contrary to the requirements of the decision by the Enlarged Board of Appeal G2/10). Note that the Board of Appeals does not discuss the other criteria for eligibility of such a disclaimer (and especially its compliance with Article 123(2)EPC, see point 13).

A.3. Decisions T2221/10 and T1441/13 give rise to doubt as to the "relevant date" to be taken into account in order to establish whether the invention can be developed without destroying an embryo. Where decision T2221/10 discusses "the relevant date of the application" in a general manner, decision T1441/13 suggests that it is the priority date of the application (see point 10). If that is the case, applications submitted after 10 January 2008 but claiming priority for an application before that date, should be rejected in accordance with Article 53(a)EPC. Also, these applications could be refused the benefit of their priority claim since, at that date, no patentable embodiment of the invention was
reproducible.

A.4. Like hESCs lines, other human pluripotent stem cells could be considered to be patentable in the future. These are pluripotent cells derived from human “parthenotes”, unfertilised eggs which, by parthenogenesis, are induced to divide and to develop. These oocytes only contain maternal DNA but not paternal DNA, which means that without genetic manipulation, they are unable to develop into a human being.

In its decision of 18 October 2011\(^1\), the ECJ issued a wide definition of the term “embryo” to mean “any cell with the capacity to develop into a human being”, including “any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis”, therefore, in other words, a parthenote. Thereafter, inventions involving the destruction of parthenotes or cells obtained by destroying them, were systematically rejected by the EPO in accordance with Article 53(a)EPC.

The ECJ however recently revised the definition of the “embryo”. Referred to by the UK High Court about an application from the company International Stem Cell Corporation (ISCO), the ECJ considered, on 18 December 2014\(^2\), that, to be qualified as a “human embryo”, an organism must necessarily have the “intrinsic ability to develop into a human being”. Consequently, a parthenote is not a “human embryo” as (and as long as) it does not have this “intrinsic ability to develop into a human being”.

Although the EPO does not have the obligation to adopt this definition, we anticipate, thanks to the turnaround in case-law in the European Union, that it should be easier to protect technologies using human parthenotes in the future in Europe, including those involving their destruction.

B. Human embryonic stem cell patentability in the United States

B.1. Until 2012, the United States Patent and Trademark Office (USPTO) granted patents protecting human pluripotent cells, and in particular hESC lines (see US patent 7,029,913 by the WARF foundation, issued in 2006).

\(^{1}\) Brüstle v. Greenpeace decision, C-34/10, 18 October 2011, see our article of 14 February 2012
\(^{2}\) ISCO v. Controller General of Patents decision, C-364/13, 18 December 2014
However, the recent decisions by the Supreme Court (Association for Molecular Pathology v. Myriad Genetics Inc, 2013 and Mayo Collaborative Services v. Prometheus Laboratories, Inc, 2012\(^3\)) brought into question the patentability of “products of nature”, and especially of cells such as embryonic stem cells.

The latest Guidelines issued on 16 December 2014 by the USPTO (2014 Interim Guidance on patent subject-matter eligibility) are very clear on this subject: a claim covering a “human-induced isolated human heart cell” is not “patent-eligible” according to the terms of Article 35 U.S.C. § 101 (see example 9). In effect, it is not because a cell is “isolated” from its natural “human-induced” environment that it is different from those occurring naturally. A cell can only be considered to be patentable if it is “significantly different” from natural cells. This difference may concern the structure, function or other aspect.

B.2. However, it should be noted that the usefulness of embryonic stem cells resides precisely in the fact that they have the same properties as “natural” stem cells (if not, they would have a lot less research and medical potential).

Would it be enough to add a plasmid, a marker, or an artificial gene to hESC to render these cells patent-eligible, even if these exogenous elements change neither their function nor their behaviour?

Where induced pluripotent cells (iPS) are generally obtained by artificial genetic constructions, hESC line production generally involves isolation of embryonic cells and their culture in a special medium. Yet, if no genetic modification is required during hESC production, how can they be differentiated from “natural” stem cells? Is a hESC composition containing a large number of cells, “patent-eligible” because it is impossible to find “naturally” a composition containing such a large number of cells at the same (early) stage of differentiation?

Today it is difficult to identify the characteristics that would have a sufficient effect on the structure or function of hESCs to induce a “notable difference” according to the terms of the USPTO's Guidelines, without this affecting their therapeutic interest. It would be useful to evaluate in a few months' time how the USPTO examiners will assess this “difference” in this highly specific technical field.

\(^3\) See our articles of 1 July 2013 and 25 June 2014 respectively
We are here to provide any further information you may require on this topic, and to advise you, on a case-by-case basis, of the most suitable strategy for your situation. Do not hesitate to get in touch with your usual contacts at REGIMBEAU.

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