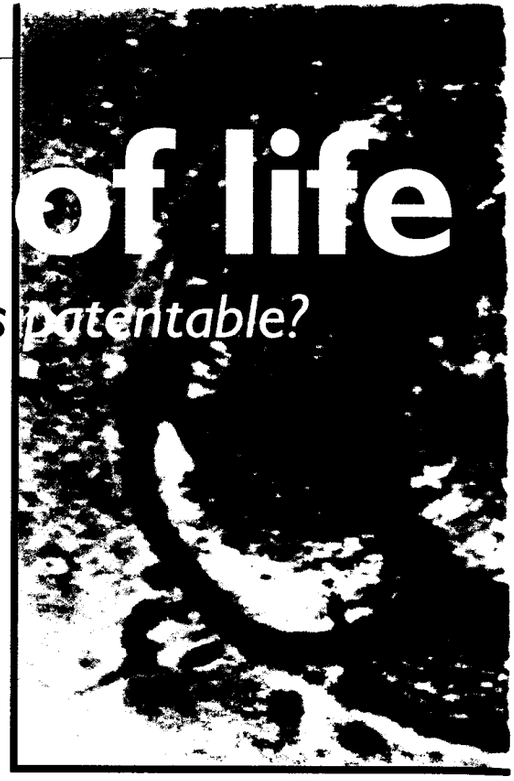
The value of life

Are human embryonic stem cells patentable?



Claudio Germinario, of Società Italiana Brevetti, considers the arguments that may be relevant to a pending European Patent Office appeal on the patentability of embryonic stem cells

Pluripotent stem cells of embryonic origin (ES cells) are the magic tools able to produce almost all cell types in the body. For this reason, research nowadays is focusing on embryonic stem cells as the most ductile means for future therapies. The question, however, remains whether embryonic stem cells will be considered suitable for patent protection under the European Patent Convention (EPC) and under the different national systems of European Union member states.

So far, experts have taken differing and sometimes contradictory stands. The European Group on Ethics (EGE) suggests in its Opinion number 16 of 7 May 2002 that: Isolated ES cells, freshly derived from human embryos, and unmodified cell lines established by ES cells would appear not to be patentable, especially because they are undifferentiated and consequently they cannot be said to have a defined industrial application. Moreover, they are so close to the human embryo they have been isolated from, that their patenting may be considered a form of commercialisation of the human body.

On this basis, modified (or differentiated) human ES cell lines propagated *in vitro* would appear to be patentable, since they have acquired useful characteristics which define a specific industrial application.

The EGE finds, however, that there is no ethical bar to the patentability of processes involving human ES cells, whatever their source. In particular the EGE considers that the patenting of inventions allowing the transformation of unmodified human ES cells into genetically modified ES cell lines or into specifically differentiated cell lines is ethically acceptable.

On the other hand, the European Patent Office (EPO) seems to have taken, for the moment, a more cautious stand. For instance, the Opposition Division competent in case EP-B- 695 351 (*University of Edinburgh* case), expressed the opinion that patent protection should be refused not only for any type of human embryonic cells (totipotent, pluripotent, multipotent), but also for processes involving the use of human ES cells for the production of modified ES cells.

An appeal was lodged against the Opposition Division ruling, which is now pending before the Board of Appeal of the EPO. However, since a final decision is not to be expected in the very near future, one could try to predict possible arguments which may be relevant for the outcome of the appeal; mainly based on the legal context defined by Directive 98/44/EC (the Directive) on the legal protection of biotechnological inventions, by the European Patent Convention (EPC) and by the Case Law of the Boards of Appeal of the EPO.

In summary

- For all the research and development a question remains as to whether embryonic stem cells will be considered for patent protection under the European Patent Convention (EPC)
- Opinion is divided. The European Group on Ethics believes that there is an argument for patentability, whilst the European Patent Office (EPO) has, so far, taken a cautious approach
- A pending appeal at the EPO could have an impact, but the ruling is not expected in the very near future. The author tries to predict possible arguments

The legal context

The first explicit provisions that may represent a bar to the patent protection of human ES cells, and ES cell lines and processes involving human ES cells, are set out by Rule 23e (1) EPC which reads: *"The human body, at the various stages of its formation and development, and the simple discovery of one of its elements ... cannot constitute a patentable invention"*.

Rule 23e (1) EPC together with Art. 5 and Recital (16) of the Directive defines a direct evolutionary line between germ cells and the fully developed human being. Each step of this line identifies an entity (ie, fertilized oocyte, morula, blastocyst, foetus and so on) capable of developing into a human body and therefore represents a stage of the human body formation excluded from patentability.

Therefore, the decisive element to be considered while assessing the patentability of human embryonic stem cells is not its proximity to the very concept of human embryo or human body, but its capability or incapability of generating a complete human body.

It is known that totipotent ES cells are able to form all the types of tissues needed for the support and development of the foetus, including the placenta, and therefore of the complete human body. So there appears to be no doubt on the exclusion from patentability of this type of ES cell.

Unlike totipotent cells, pluripotent ES cells are able to give rise to many, but not all, cell types necessary for foetal development. For example, they are not able to form placental tissue. In this case, it is the system consisting of pluripotent cells plus placental tissue or placental environment, seen as a whole, that can be considered as a stage of the human body formation, while the pluripotent cells, taken alone outside their native and temporary specific environment, would appear to be unable to develop into a complete human body. If this proves scientifically correct, pluripotent cells, in isolated form, can hardly be said to represent a stage of the evolutionary pathway envisaged by Rule 23e (1) EPC. Accordingly their exclusion from patentability under the provision of this Rule seems to be very questionable.

The same considerations apply, of course, to multipotent stem cells, which already exhibit a considerable level of specialisation. For this reason, they are committed to form specific types of tissues with particular functions, but definitely not all the tissues forming the human body.

In so far as pluripotent and multipotent ES cells and cell lines are not excluded from

patentability by virtue of Rule 23e (1) EPC or Art. 5 (1) of the Directive, they should not even be excluded on the grounds that they are in unmodified form.

There is no doubt that *in vitro* produced pluripotent and multipotent ES cell and cell lines are "elements isolated from the human body" within the meaning of Rule 23e (2) EPC. This rule, like Art.5(2) of the Directive, lays down that:

> *"an element isolated from the human body or produced by means of a technical process... may constitute a patentable invention even if the structure of that element is identical to that of a natural element."*

Thus, Rule 23e EPC and the Directive's Art. 5(2) recognise the implicit difference between "a natural element" in its natural environment, ie, the human body, and "an isolated element" extracted from its natural environment.

The same principle is reiterated, in relation to biological material, by Rule 23c(a) EPC, which provides that:

> *"Biotechnological inventions shall also be patentable if they concern biological material, which is isolated from its natural environment or produced by means of a technical process even if previously occurred in nature".*

It is worth stressing here that ES cell lines fall within the definition given by the EPC (Rule 23b (3)) or by the Directive of "biological material"; that is "any material containing genetic information and capable of reproducing itself".

Under these circumstances, the question of whether *in vitro* isolated ES cells are modified, in the sense of integrating a novel genetic tract, or unmodified is completely immaterial to the patentability of the same. In fact, the technical process of obtaining the cells in isolated individualised form and propagating them *in vitro* in order to produce usable cell lines, renders the cells inherently "modified", thus novel, as regard to the natural cells when surrounded by their natural context, ie, the embryo.

Thus the first conclusion suggested here is that neither Rule 23e (1) EPC nor the Directive's Art 5.1 should be interpreted as excluding from patent protection pluripotent or multipotent ES cells, even in unmodified form.

Double morality?

The second explicit provision that may represent a bar to the patent protection of human ES cells, and cell lines and processes involving human ES cells, is set out in Rule 23d (c) EPC, which excludes inventions involving the use of human embryos for industrial or commercial purposes.

The EGE finds, however, that there is no ethical bar to the patentability of processes involving human ES cells, whatever their source

Although this exclusion relates to a use, thus to an activity, not a product, it may have an important limiting effect on the patentability of the ES cells and cell lines as such.

Two considerations deserve credit.

Isolated human ES cells, for which patent protection may be sought, can only be obtained by destroying a human embryo. This action would amount to the "use of a human embryo for industrial or commercial purposes". Hence, since the process of producing isolated ES cell lines necessarily includes a procedural step that is excluded from patentability as ethically unacceptable, the very product of such a process would also appear to be excluded for the same reason. In fact, the "invention", whether directed to a product or a process, would in any case concern or involve the prohibited use of a human embryo. Arguing that the result of the "invention" is a technically modified cell does not solve the problem, since the starting point would still be the destruction of an embryo.

In consideration of these arguments, it is important to bear in mind a basic principle of patent protection. The scope of the protection conferred by a patent is given by the wording of the claims, interpreted, if need be, in the light of the description (Article 69 EPC). However, this interpretation can never have the effect of arbitrarily integrating into the scope of the protection specific subject-matter, either activities or products, that the applicant had voluntarily excluded from the wording of the claims and accordingly from the scope of protection.

This principle is of the utmost importance while considering the patentability of claims directed to a process of producing unmodified or modified ES cell lines from freshly obtained ES cells, and claims directed to the cell lines thus obtained. If the process claim defines a process starting from embryonic cells or cell mixtures, already in single disaggregated form, without citing or claiming any preliminary step of producing freshly disaggregated cells by destroying a human embryo, then this "prohibited" step cannot be regarded as comprised within the scope of protection. Accordingly, any inter-pretation intended to arbitrarily integrate this step within the ambit of the claim and declare the claim unpatentable in its entirety on the grounds that it is ethically unacceptable, would appear to be untenable.

Although admittedly any such process must begin with the destruction of a human embryo, this would appear to be immaterial to the patenting of the process and cell lines thus obtained in so far as the "prohibited" step is not claimed. In the same way, a method for gaining biological material, say a protein, from corpses does not appear to give rise to particular ethical concern, regardless of which circumstances produced the cadaver – the obtaining of the corpse simply not being a part of the invention.

This approach envisages a sort of "double morality", as already recognised by the EGE, which observes in Opinion 16, page 13, last paragraph: "One could expect that to consider research on human embryos for the purpose of obtaining stem cells as unethical, might imply the prohibition of the import for research of embryonic stem cells derived from human embryos..., which is not always the case".

As a matter of fact, while national laws of nearly all European Union states bar the creation of human embryos for research purposes and as a source of stem cells, many EU states (Finland, Greece, the Netherlands, Sweden and the United Kingdom) allow human ES cells to be taken from supernumerary embryos, whereas many other states either do allow (Germany), or at least do not explicitly prohibit, the importation of human ES cell lines from other states (see *Report on Human Embryonic Stem Cell Research*, the Commission of the European Communities, SEC(2003) 441, 3 April 2003).

Under these circumstances, a process of treating human ES cells does not necessarily need to comprise the prohibited stage of producing the first generation of freshly disaggregated embryonic cells, since these disaggregated cells are already available through legal importation or from many other sources.

The varied picture made up by the different national laws justifies the pragmatic view of the EGE; there is no ethical obstacle to the patentability of *in vitro* modified stem cells and processes involving human stem cells, whatever their source (see Opinion 16, page 15 item 2.3, first and last paragraphs), which position actually amounts to accepting the principle of "double morality".

Another bar to the patentability of ES cells may be envisaged in that embryonic cells freshly obtained from a human embryo may be considered inherently or "ethically" equivalent to the embryo as a whole. Therefore all the limitations relating to the latter (ie, use for commercial purposes) would also apply to the former.

The Opposition Division in case EP-B-695 351 (*University of Edinburgh*), gave credit to this interpretation and held that Rule 23d(c) EPC *"has to be interpreted broadly to encompass [the exclusion of] not only the industrial and commercial use of human embryos, but also the human cells retrieved therefrom by destruction of human embryos"*. On this ground, the Opposition Division rejected all the methods of isolating embryonic cells and all the embryonic cells thus obtained, although in modified form.

This position, however, would appear to be in breach of EPO case law. In decision T 0356/93 (Plant cells/Plant Genetic System – OJ EPO) the competent Board of Appeal considered the patentability of modified plant and plant cells and the process for producing the same.

In summary, the appellant, Greenpeace, had argued that the claims for modified plants were not patentable because their definition covered plant varieties, which were excluded from patent protection by virtue of Art. 53 (b) EPC, and that the claims for modified plant cells were also not patentable because a plant cell, being capable of regenerating a complete plant, must be considered equivalent to the plant itself.

The Board, while upholding the appellant's first argument that plants were not patentable – the protection conferred also covered plant varieties – rejected the appellant's arguments based on the alleged equivalence between plant and plant-cells, finding that:

> *"Plant cells, as such, which modern technology allows to culture much like bacteria and yeasts, cannot be considered to fall under the definition of a plant or a plant variety. In this respect, it is further noted that plant cells are considered to be microbiological products in the broad sense under the current practice of the EPO" (point 22, page 31);*

and that,

> *"As for claim 14, which relates to plant cells, the Board cannot agree with the appellant's submission that this claim covers de facto plant varieties and that for this reason, it is not allowable under Article 53(b) EPC, because, as already stated, plant cells as such may not be considered to fall under the definition of a plant or a plant variety. Thus the subject-matter of claim 14 does not represent an exception to patentability under Article 53(b) EPC". (point 40.2, page 40)*

In conclusion, the Board of Appeal denied the asserted equivalence between a whole entity, ie, a plant, and the cells retrieved from this entity (though capable of regenerating the entity), and consequently rejected the argument according to which the exclusion from patentability of a whole entity extends directly to the isolated cells obtained therefrom.

These principles would appear to apply *mutatis mutandis* to Rule 23d (c) EPC, with the result that a broad interpretation of this Rule to exclude also the use of ES cells would appear to be completely unjustified.

Finally, the broad construction of Rule 23d (c) EPC given by the Opposition Division in the above *University of Edinburgh* case would also appear to be in contradiction with another general principle, confirmed in several cases by the Boards of Appeal of the EPO: that any exclusion from patentability represents an exception to the general rule, and as such must be interpreted narrowly (see T 320/87 or T 19/90).

In the light of the above, it is suggested here that neither Rule 23 d (c) EPC nor the Directive's Art 5.1 should be interpreted as excluding from patentability pluripotent or multipotent ES cells and cell lines as such.

No other explicit limitations are to be found in the EPC or in the Directive. Limitations may only be envisaged as inherent in the general principles laid down by Article 53 (a) EPC, or Article 6.1 and Recitals 16, 38 and 42 of the Directive. It is evident, in fact, that the list of exclusions in Rule 23d EPCR and Article 6.2 of the Directive is not exhaustive. For this reason, any future interpretation intended to exclude from patentability further specific objects, such as ES cells, would appear to be possible. However, since this decision would be in breach of the presently valid principles of patentability it should preferably be left to the competence of the legislator. ■

About the author

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