Patentability of inventions involving human stem cells in Europe

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Abstract

In the last two years, research into stem cells has raised extraordinary therapeutic hopes – such as regenerative medicine – but also strong ethical questions. These questions have been fuelled by announcements, from private companies in particular, of the possibilities for human cloning. One of these questions relates to the patentability of inventions resulting from this area of research. In Europe this question is linked to the general debate surrounding the patentability of biological materials, such as genomic sequences. Although a large number of applications have been filed these last years, a few patents have already been issued. Some of them have been opposed at the European Patent Office. At the request of the European Commission, the European Group on Ethics (EGE) has prepared an opinion on ethical aspects of patenting inventions resulting from human stem cell research.

The opinions expressed in this paper are the personal views of the author and do not in any way represent official views of the company.

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INTRODUCTION

2001 was a very intensive year in the stem cells field and related domains. The highpoint was probably reached in August with the publication by the National Institutes of Health (NIH) of the list of the 64 cell lines derived from human embryonic stem cells that met the President Bush criteria.[1]

Another event was the preliminary announcement by Advanced Cell Technology Inc. of the cloning of human embryos.[2] Technically adult stem cells have become competitors of embryonic stem cells, although there is no agreement that either of these groups could be a definitive candidate for therapeutic applications.

Finally the autumn of 2001 and the beginning of 2002 saw the implementation in some European countries of dissimilar laws relating to embryo research and the beginning of a draft of an international treaty on ban of human being cloning.

In this rather volatile situation it is very difficult to have a clear view of the technical and legal landscape surrounding stem cells – embryonic stem cells in particular.

Although relating to another field, opposition to the Myriad patents has drawn public attention to the potential impact of patents on public health. It has probably strengthened the concern of some scientists regarding patents.

It is the aim of this paper to summarise the current patent situation in Europe, and to try to anticipate what the situation could be tomorrow.

THE CURRENT LEGAL PROVISIONS IN EUROPE

General legal provisions of patent laws, including provisions relating to the protection of drugs, can be applied to inventions involving human cells. Human or hybrid cells have been patentable in Europe for a certain number of years. For example patent EP 0 033 579 issued in 1985[3] relates to hybridoma cell lines.

Directive 98/44/EC on the legal protection of biotechnological inventions has recently confirmed this situation.[4]

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Stem cells are not specifically mentioned in the EC Directive

Article 3.2 of this Directive states that biological material that is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it has previously occurred in nature. Article 5.2 states that an element isolated from the human body or otherwise produced by means of a technical process may constitute a patentable invention.

More specific provisions can be found in the Directive 98/44/EC relating to the deposit of biological material. Thus where an invention involves biological material, such as cells, that is not available to the public and that cannot be described in such a manner as to enable the invention to be reproduced by a person skilled in the art, the biological material should have been deposited with a recognised depositary institution, such as the one that acquired this status by virtue of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purpose of patent procedure. It should be noted that such provisions already existed in European national laws, and in the European Patent Convention (EPC) as well.

This Directive has been integrated almost identically into the implementing regulations to the EPC,[5] but is still implemented in only some of the member states.

Various types of stem cells are known

Stem cells are not specifically mentioned per se in this Directive. However, Article 6 states that 'inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality' and gives examples of inventions which should be considered as unpatentable, such as:

- processes for cloning human beings;
- processes for modifying the germ line genetic identity of human beings;
- uses of human embryos for industrial or commercial purposes.

The reason why stem cells were not considered when the Directive was drafted can be explained by the very recent progress in this field. Indeed it was only in 1998 that the first human embryonic stem cells were isolated. Furthermore the debate around the Directive was focused on other subjects such as the patentability of gene sequences, which with the human genome sequencing, was a hotter subject.

IS THE LEGAL SITUATION IDENTICAL FOR ANY KIND OF STEM CELL?

A stem cell is defined as a cell that can divide to produce either cells like itself (self-renewal), or cells of one or several specific differentiated types. Stem cells are not yet fully differentiated and therefore can reconstitute one or several types of tissues. Depending on their origin stem cells are pluripotent (embryonic stem cells) or only multipotent (for example skin stem cells). Some human stem cells have already proved their therapeutic potential in humans.

Transplantation of human haematopoietic stem cells, of adult or foetal origin, is routinely used to restore the production of blood cells in people affected by leukaemia or aplastic anaemia after chemotherapy. Marrow stem cells genetically engineered (infected *ex vivo*) with a retrovirus encoding γc cytokine receptor have also been used successfully for treating babies having severe immunodeficiency X1 disease.[6]

Very interesting – although preliminary – results have furthermore been obtained in regenerative medicine with the treatment of some patients with Parkinson's disease using human foetal neural stem cells.

There are various types of stem cells currently known that could be considered for therapeutic purposes:

- foetal stem cells;
- adult stem cells from the person to be treated;

- embryonic stem cells from 'normal embryo';
- embryonic stem cells resulting from the replacement of the nucleus in an oocyte (therapeutic cloning);
- cell lines having embryonic origin, modified to avoid immune rejection;
- stem cells obtained from embryos created by parthenogenesis.

The various types of stem cells raise different issues, such as ethical issues

Whether adult stem cells or embryonic stem cells would be employed is still not clear. Many scientists contend that research must continue on both types, since both have drawbacks and advantages. Briefly, adult stem cells would have limited pluripotency compared with embryonic stem cells, and are at the moment much more difficult to isolate in large quantities. But on the other hand embryonic stem cells raise ethical issues since it is necessary to destroy a living embryo to obtain them, and furthermore they would be rejected by the immune system, unless they were modified.

Embryonic stem cells can also be used for therapeutic cloning (and also reproductive cloning). In cloning, the genetic material from the egg is removed and replaced with that of an adult cell. Thus the embryo obtained by this nuclear substitution is an almost perfect copy (except for the mitochondria) of the person having given the adult cell. Embryonic cells obtained in this way should not be rejected by the immune system of the donor.

A very recent approach – not yet tested with human cells – is the creation of embryo-like structures by parthenogenesis. The so-called parthenotes have been obtained by subjecting mammal eggs to chemical treatments so that they develop as if they had been fertilised (see in particular the patent application WO 01/30 978 filed by the University of Massachusetts[7]). This process could avoid ethical problems raised by the use of true embryo stem cells. But it is not clear whether these structures would avoid the embryo status. Indeed an embryo is defined as being the result of the fertilisation of an egg by sperm, and thus contains genetic material from both mother and father. Parthenotes would only contain genetic material from the mother.

These various stem cell types raise different patent issues, both on the strength of their protection by the patent system and ethical issues.

One of the most important issues, which can be raised for any kind of cells, is their protection per se, ie as products. The issue is of importance since product patents are generally much easier to enforce than process patents. Indeed for enforcing process patents it is necessary to show that the products have been obtained directly by the patented process. Although the burden of proof can be reversed in some countries, it can be difficult for the patentee to show that the alleged infringer has really used the patented process to obtain the product, ie the cells.

One of the obstacles to the therapeutic use of stem cells lies in the immunorejection processes. It means that the use of cell lines is currently not considered as an option. The only cells that could be used would be those of the patients themselves. It would be difficult, although not impossible, to protect such cells per se, because of the difficulties of characterising these cells.

Claim 1 of the application EP 0 770 125 (8) illustrates this problem:

> A purified preparation of primate embryonic stem cells which (i) is capable of proliferation in an in vitro culture for over one year, (ii) maintains a normal karyotype through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) will not differentiate when cultured on a fibroblast feeder layer.

Another approach could consist of modifying stem cell lines to evade attack by the immune system. In such a case of patenting cell lines could provide an efficient protection.

The most important issues are the ethical ones, and in particular those arising from the embryonic stem cells.

Embryonic stem cells raise the most important ethical issues

THE SPECIFIC ISSUES RAISED BY THE EMBRYONIC STEM CELLS

As indicated above, Article 6.2 recites examples of what should be considered as unpatentable, namely Paragraph (a) processes for cloning human beings, and Paragraph (c) use of embryos for commercial purposes.

Could Paragraph (a) be opposed to therapeutic cloning? As explained in the previous section, therapeutic cloning comprises the replacement of the nucleus of the oocyte by the nucleus of an adult cell. The first steps are the same as the first steps in reproductive cloning. But the final results of the two processes are clearly different, and it would be easy to point out this difference in a patent. Thus it is arguable that therapeutic cloning does not fall under the provisions of Paragraph (a) since it does not result in reproductive cloning, the process being stopped by the destruction of the embryo to recover the embryonic cells.

Only a few patents have been granted by the EPO

Could the use of embryos to obtain stem cells be considered as falling under Paragraph (c)? This paragraph relates to embryos per se and does not mention embryonic stem cells. In 1997, when the final version of the directive was drafted, the first human embryonic stem cells had not been isolated, which may explain this.

This raises a question: could this paragraph apply to part of the embryo, ie the embryonic stem cells? A comparison can be made with the sale of proteins isolated from blood. Their sale would not appear as contrary to morality, which, of course, would not be the case of the sale of the donor.

Furthermore, according to a general principle of law, exclusions – and in the present case exclusions of Paragraphs (a) and (c) – are to be construed narrowly. Following this principle, stem cells, including embryonic stem cells, should not be considered, at least on the basis of these two paragraphs, as unpatentable per se.

The interpretation of Paragraph (c) also raises a definition issue: what should be considered as an embryo? For example should a parthenote be considered as an embryo? The response is far from easy. The European Group on Ethics (EGE) opinion, discussed below, brings responses to certain questions but does not clarify the definition issue.

CURRENT OPPOSITION AT THE EUROPEAN PATENT OFFICE

Few patents have been issued by the European Patent Office (EPO), because of its general backlog in biotechnology, but also because of the office's moratorium on the applications relating to stem cells. Opposition has been filed against only a couple of these issued patents.

One of the most advanced opposition has been filed against the patent EP 0 343 217 issued in 1996 to Biocyte Corp.,[9] a US company. This patent related to the less controversial foetal or neonatal haematopoietic stem cells, in particular from cord blood. The claims were directed to a composition comprising these cells and a cryopreservative, and the use of this composition for the manufacture of a medicament for the treatment of Fanconi's anaemia.

The opponents filed the opposition on various grounds, including novelty and inventive step. The opposition division agreed with the opponents and revoked the patent on these grounds. The opponents also tried to revoke the patent for other grounds – as is usual in this kind of procedure – and in particular by arguing that the invention was contrary to '*ordre public*' or morality (Article 53(a) EPC).

The opposition division considered in

its decision that Article 53(a) EPC was a provision that could only apply in very exceptional cases, and that for this provision to be applied the invention had to be in clear conflict with legal or ethical values and such a conflict had to exist with all uses of the invention as claimed. The division added that 'the recovery of blood from the umbilical cord of newborns is not illegal since it is not forbidden by law nor it is unethical', that until shortly before the filing date the cord blood, as well as the umbilical cord itself, was discarded, and furthermore that the recovery of umbilical cord blood may now be potentially of great utility. It concluded that for these reasons Article 53(a) EPC could not apply and it did not need to decide whether specific uses of the invention – such as possibly the recovery of foetal blood *in utero* – could give rise to moral objections.

Oppositions have been filed against a couple of patents

An appeal has been filed at the EPO Board of Appeal. No date has been decided for the oral proceedings.

To be noted is an opposition against the patent EP 0 341 966 granted to Stanford University.[10] The decision to revoke this patent (applied in 1988) was taken in 1999.

Although not directly related to stem cells another opposition against the Stanford University patent EP 0 322 240[11] is to be noted. As in the previous example this patent has been challenged by three opponents on various grounds, including Article 53(a) EPC provisions. This patent had been granted for chimeric non-human animals comprising xenogenic organ or tissue. The opponents *inter alia* argued that the invention was unethical and against the general moral principles of Western society. The EPO maintained the patent and justified its decision by stating that 'there is at present no consensus in Europe society about the desirability or otherwise of this technology, and public opinion is still being formed on this and related matters. It would be presumptuous for the EPO to interfere in this public debate'.

The rationale of this EPO decision could be applied to therapeutic cloning on which the European society is far from having reached a consensus, but for which the medical benefits conferred by the invention are not in dispute.

In the UK the allowance of two patents has sparked protests.[12] GB 2 331 751[13] was filed in 1995 under the name of three applicants including the Roslin Institute, which was bought in 1999 by Geron Corp., a Californian company. The UK patent office allowed this patent with claim 1 drafted as follows: 'A reconstituted animal embryo, prepared by transferring the nucleus of a quiescent diploid donor into a suitable recipient cell, wherein the animal embryo is at a developmental stage up to the blastocyst stage'. A parallel patent was allowed for a method of reconstituting such embryos, which was the technique used to produce Dolly, the first cloned sheep. The claims, not limited to any particular animal species, were considered as encompassing human. The corresponding European patent, as well as the US patent, was also granted but with claims limited to non-human embryos, and was not submitted to an opposition.

The last example of a patent relating to stem cells and being opposed is patent EP 0 695 351[14] filed by the University of Edinburgh, and exclusively licensed to Stem Cell Sciences, an Australian company. This patent, granted in 1999, has been opposed by 14 opponents.

Claim 48 reads as follows:

> A method of preparing a transgenic animal, . . . comprising:
>
> – providing a blastocyst;
>
> – providing animal cells according to any of claims 37–38;
>
> – introducing the animal cells into the blastocyst;
>
> – transferring the blastocyst to a recipient; and

– allowing an embryo to develop to a chimearia animal to enable germline transmission of the selectable marker.

It is specified on page 2 that the term animal cell is intended to embrace all animal cells, including *human* cells.

In a declaration the EPO admitted that it erroneously granted the patent and acknowledged that 'the term ''animal'' also includes ''human''' but it was too late; the patent had been issued. Although it is likely that the patent will be at least limited – if not revoked – the debate will be passionate since Greenpeace, in order to protest against the issuance of this patent, bricked up the entrance of the EPO in Munich!

The European Group on Ethics has given an opinion on the patentability of stem cells

Opponents argued furthermore that the invention was not reproducible on human cells at the date of filing of the application.

Geron has also some rights on patents filed under the name of the Wisconsin Alumni Research Foundation (WARF), which relate to purified preparations of pluripotent human embryonic stem cells. The issuance of the US patent raised some concerns among the scientists. The examination of the corresponding European application is still on hold.

THE EGE OPINION

At the request of the European Commission, the EGE has prepared an opinion on ethical aspects of patenting inventions resulting from human stem cell research. This group advises the European Commission on ethical aspects of science and new technologies in connection with the preparation and implementation of Community legislation or policies. It already gave an opinion published in November 2000[15] on the ethical aspects of human stem cell research and use.

Preliminary debates with concerned people from ethical groups, industries and patent office representatives, religious representatives, scientists, etc., were very intense and were in a large part focused on embryonic stem cells. Concerns were ethical and research-oriented. In the latter case the concern was 'would the patents block the European research?'

Although not specific to research on stem cells, research-oriented concerns could be easily answered by the provisions included in the national laws of European countries relating to exemptions for research purposes. For example article L 613-5 of the French code of industrial property states that 'The rights conferred by the patent do not cover. . ..(b) acts performed for experimental purposes relating to the subject matter of the patented invention.' In this regard the debate is not different from the debate around the patentability of human genomic sequences.

The EPO has put the whole field of embryonic stem cells on hold and is currently waiting for the recommendations of the EGE before going on with the examination of applications relating to embryonic stem cells.

The opinion of the EGE on patentability was given on 7th May, 2002, and is available on the EGE web site.[16] In its opinion the EGE states that the option to forbid patenting of stem cells or stem cell lines has been considered, but has not been adopted because the consequence of such an option would be the major slowing of this research field. Furthermore it would be contrary to the EU choices as expressed by the 1998 EU Directive.

However, it is the opinion of the EGE that:

> **Isolated stem cells** which have not been modified do not, as product, fulfil the legal requirements, especially with regards to industrial applications, to be seen as patentable. In addition, such isolated cells are so close to the human body, to the foetus or to the embryo they have been isolated from, that their patenting may be considered as a form of commercialisation of the human body.

- When unmodified stem **cell lines** are established, they can hardly be considered as a patentable product. Such unmodified stem cell lines do not have indeed one specific use but a very large range of potential undetermined uses. Therefore, to patent such unmodified stem cell lines would also lead to too broad patents.

- Therefore only **stem cell lines which have been modified by *in vitro* treatments or genetically modified** so that they have acquired characteristics for specific industrial application, fulfil the legal requirements for patentability.

- As to the patentability of **processes involving human stem cells, whatever their source**, there is no specific ethical obstacle, in so far as they fulfil the requirements of patentability (novelty, inventive step and industrial application).

Despite legal uncertainties, various claims can be considered

In particular the EGE considered that patenting inventions that allow the transformation of unmodified stem cells from human embryonic origin into genetically modified stem cell lines or specific differentiated stem cell lines for specific therapeutic or other uses, is ethically acceptable. But the Group called for 'a cautious approach, excluding the patentability of the process of creation of a human embryo by cloning for stem cells'.

One of the EGE members emitted a dissident opinion. Although they generally agreed with the above, they did not agree with 'permitting patenting processes and products using material resulting from destroyed human embryos'. At last the EGE considered that 'applicants for a patent involving human stem cells should declare which is the source of the stem cells'.

Thus the EGE considers most of the cell preparations – whether established or not – should not be patentable, with the notable exception of engineered stem cells lines, whereas processes – except cloning processes – should be considered as patentable. This opinion, which mixes ethical, research and patent considerations, is only advisory. It is too early to determine to what extent the patent offices – European or national – will apply these recommendations.

Table: Possible claims for inventions relating to human stem cells

Despite legal uncertainties, it is possible to consider general types of claims that could be put into European patent applications drafted for inventions relating to stem cells. Of course these claims should be adapted according to the invention and to the prior art, and furthermore to ethical considerations. Roughly the following claims could be drafted.

Product claims
- Human stem cells characterised by their cell type composition.
- A composition comprising human stem cells and an additive.
- Cell line.

Therapeutical claims
- A composition comprising human stem cells characterised . . . for use as a medicine.
- Use of a composition comprising human stem cells characterised. . .for the manufacture of a medicament for the treatment of a given disease.

Production process claims
- A method for isolating/enriching human stem cells characterised. . ..
- A method for maintaining human stem cells in vitro characterised. . ..
- A method for preserving human stem cells characterised. . ..

Screening process claims
- A method for screening drugs comprising contacting human stem cells with the drug to be tested. . ..

CONCLUSIONS

Various types of stem cells are currently considered for regenerative medicine in particular. None of the various solutions proposed seems to reach a consensus among the scientists. These several solutions raise various legal issues, such as the difficulty to protect the cells per se and the limited protection conferred by the process patents used to obtain them.

Embryonic stem cells – which are currently considered as the most promising cell type – raise the most crucial issues.

The recently given EGE opinion recommends that the stem cells – embryonic or non-embryonic – be considered as non-patentable, except if they have been modified by *in vitro* treatments or genetically modified. It recommends, however, that processes involving stem cells, whatever their source, be patentable, except cloning processes.

It is probably too early to determine to what extent the patent offices (European or national) will apply these recommendations. But if strictly applied this opinion could have some undesirable consequences on this research area.

The protection conferred by the patents in Europe is already considered as limited, compared to USA, by interested circles in particular because of the impossibility to protect the methods of treatment. Further limiting the scope of protection would limit private research investments in this promising domain – where European industry still has a chance – and would encourage companies to keep their research results secret.

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