Stem cell patenting

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Abstract

The patenting of embryonic stem cell-related inventions appears to be as controversial as the technology itself. The author outlines the state of play in Europe and the USA as well as other selected territories. While Europe has the broadest statutory exclusions to patenting of inventions which might be regarded as unethical, it appears that a smooth ride for applicants and patent holders is not guaranteed elsewhere.

INTRODUCTION

Stem cell technology is one of those areas of science that is no longer solely the domain of scientists. Operating as it does at the boundary between medicine and ethics it has attracted the attention of a much wider public. On the one hand there is the fantastic potential to cure debilitating human diseases such as Parkinson's, Alzheimer's and diabetes, and on the other the inevitable association of stem cell research with the creation and manipulation of human embryos.

'Stem cell' is in fact a very broad term encompassing any undifferentiated cell that, when it divides, can either differentiate into a particular type of tissue or remain as a self-renewing daughter stem cell. This includes cells that are designated 'pluripotent' because they have the potential to differentiate into any cell in the body and those designated 'multipotent', which can differentiate into only a limited range of cell types. Pluripotent cells can be recovered from embryonic and foetal tissue while multipotent cells can be obtained from adult tissue as well. Recently, it has been reported that certain adult multipotent cells exhibit a phenomenon called 'transdifferentiation' whereby they have pluripotent properties again, so these categories may not be as distinct as first thought. Also categorised as a stem cell are cells designated 'totipotent' cells. These are the first eight or so cells of a newly fertilised egg, which have the potential to develop into a whole animal or human but lack the self-renewing quality of other stem cells. While all the above may be considered to be 'true' stem cells, in fact the term can also be used to describe other cells engineered by genetic manipulation to have 'stem cell-like' characteristics. Although, then, the term 'stem cell' does not, implicitly, mean cells isolated from an embryo, it is human embryonic stem (hES) cells that are attracting the most interest. These are currently showing the greatest medical potential since stem cells available from adult tissues are low in abundance and not as easy to culture in the laboratory. This has been a limiting factor to their use so far.

At present, there is no harmonisation across the developed world as to the extent to which human embryos may be used in medical research. Even within the European Union there are significant differences. For example, the development of hES cells from supernumerary embryos remaining after fertility treatment is permitted in Belgium, Denmark, Spain, Finland, Greece, the Netherlands, Sweden, the UK and France but not permitted in Austria, Germany, Ireland, Luxembourg, Italy and Portugal. In the UK and Belgium, it has also been permitted to create embryos by cloning for procurement of hES cells for therapeutic purposes, but only under strict licence. In the USA it is not currently permitted to create new hES cell lines if undertaking federally funded research, although this ban does not apply to the private sector or state-funded work.

The issue of funding is, of course,

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Patents needed to recoup investment

paramount. Aside from the ethical issues, realising the full medical potential of stem cells will be very expensive. As an example, the state of California has just made three billion dollars available for stem cell research. Given the level of funding needed it comes as no surprise that those involved in this work have sought patents to protect their developments and recoup the investment.

Extent of stem cell patenting

Worldwide there have been over two thousand patent applications filed involving human and non-human stem cells, about a quarter of which refer to embryonic stem cells. Quite a number of these have matured to granted patents, particularly in the USA and Japan. The applicants for these patents face a quite different legal landscape in each of the different territories in which they may apply.

EUROPE

European legal framework for patents

In Europe, an International Convention and a European Union Directive between them govern what may be patented in relation to biological inventions. Under the European Patent Convention (EPC)[1] it is possible to obtain a bundle of national patents in up to 30 European Countries via a single application at the European Patent Office (EPO). This system provides for a central examination for patentability and if found acceptable, a European Patent is granted, but the right which accrues becomes a national right after that, enforceable only through the national courts.

It should be noted that national patents can still be obtained via national patent offices as well in most of the EPC contracting states and this option is particularly relevant with respect to the UK and stem cell inventions.

Under the EPC, the criteria for patentability are that the invention must be:

- novel, ie not made available to the public by way of publication, use or in any other way;
- inventive, ie not obvious to a person skilled in the art;
- industrially applicable, ie have a specific, substantial and credible utility;
- described in an enabling manner, ie must be described completely and clearly enough for it to be carried out by one skilled in the art.

Inventions relating to the recovery, propagation and use of stem cells, as well as the cells themselves and any downstream products deriving from them, must meet all of the above criteria the same as any other invention. However, in addition to the above positive requirements under the EPC there are certain exclusions to patentability, of which particularly pertinent to stem cell inventions is Article 53(a) which reads as follows:

European Patents shall not be granted in respect of:

> a) inventions the publication or exploitation of which would be contrary to 'ordre public' or morality, provided that the exploitation shall not be deemed so contrary merely because it is prohibited by law or regulation in some or all of the contracting states.

This gives the European Patent Office the power to refuse patent applications in respect of inventions it considers unethical. Over the years, opponents have tried to bring Article 53(a) to bear against European patents for transgenic animals and plants and human genes but without success. The office has always taken the view that this provision should be construed narrowly and be used to refuse patents only for inventions so abhorrent that the grant of a patent for it would be inconceivable. In particular it has refused to use Article 53(a) against technologies where there is no clear consensus across the EPC contracting states as to what is ethically acceptable in the field.

In July 1998 the European Union

The EU position

adopted Directive 98/44/EC on the legal protection of biological inventions more, colloquially known as 'The Biotech Directive'.[2] The intention of this was to harmonise the law across the member states of the European Union with respect to what should and should not be patentable biological inventions and it identifies certain products and activities which are not patentable on ethical grounds. In respect of hES cells the most relevant Directive articles are the following:

> *Article 5(1)*
> The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.
>
> *Article 6(2)(c)*
> The following, in particular, shall be considered unpatentable:
>
> (c) uses of human embryos for industrial and commercial purposes.

However, in construing these, account has to be taken of Article 5(2) which reads:

The Biotech Directive and its impact

> An element isolated from the human body or otherwise produced by a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

The Biotech Directive has always been very controversial and, to date, it is still not implemented in Luxembourg, Latvia or Lithuania. However, in 1999 the EPC rules were amended to incorporate the provisions of the Directive including Articles 5 and 6, which are now rules 23e(1) and 23d(c) respectively.

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Following the introduction of these new provisions, patent offices have had the difficult job of interpreting them. The UK Patent Office considered its position on patenting stem cells and in April 2003 set out its policy[3] as regards the patentability of processes for obtaining stem cells, human totipotent cells and human embryonic pluripotent stem cells. The office confirmed that it would not grant patents for processes for obtaining stem cells from human embryos since it regards such processes as excluded by virtue of the prohibition of uses of human embryos for industrial or commercial purposes. Neither would it grant patents for human totipotent cells since they have the potential to develop into an entire human body. However, human embryonic pluripotent stem cells that arise from further division of totipotent cells and do not have the potential to develop into an entire human body, could be patented. It was considered that these did not fall within the specific exclusions recited by the Directive and neither should they be rejected on other unspecified moral grounds in view of the enormous potential of stem cell research, including human embryonic stem cell research, to deliver new treatments for a wide range of serious diseases. Such potential meant that, on balance, the commercial exploitation of inventions concerning human embryonic pluripotent stem cells would not be contrary to public policy or morality.

Thus, hES cells that are pluripotent or multipotent and methods of propagating them are patentable in the UK providing they can satisfy the other criteria for patentability such as novelty and inventiveness. Regrettably, from the standpoint of harmonisation, the EPO has to date opted to take a different approach.

The Edinburgh Patent

The first indication of this was seen in the EPO's decision concerning European Patent EP-B 0695351 granted to the University of Edinburgh in 1999, prior to the implementation of the new rules 23e(1) and 23d(c). This EP patent is concerned with methods of isolating, enriching and selectively propagating animal stem cells. Specifically, it describes methods in which a marker gene is transfected into cell mixtures which may

or may not include stem cells, in which the marker gene is under the transcriptional control of a promoter from a gene having a stem cell-restricted expression pattern. Thus the presence of marker expression identifies the stem cells in the mixture, or depending on the marker, is able to apply a selection pressure in favour of stem cells.

The patent as granted covered the general method of selecting cells and cell mixtures transfected with the marker including stem cells. Human ES cells were not excluded. As provided for by any patent under the EPC there was an opportunity for third parties to formally oppose the grant of the patent. Fourteen parties opposed in this case, citing a number of reasons why the patent should not have been granted, including the more conventional ones such as insufficiency of disclosure, in particular that the description did not enable the methods described for any stem cells other than mouse embryonic stem cells on which the work had been done. However, all of the opponents were organisations with ethical objections to the patent, for example Greenpeace, Right to Life organisations and church organisations and so consideration of this objection formed a major part of the considerations of the office. Following the usual procedures a written decision was finally issued by the EPO in July 2003.

The patent controversy

In response to the application of the newly introduced exclusions the Opposition Division (OD) stated:

> The crucial question is whether the legislator when introducing this rule into the EPC in September 1999, has intended to ban from patenting human embryos as such or human embryos together with the cells retrieved therefrom by destruction of embryos, namely human ES cells. That is to say, the question the OD has to deal with is whether Rule 23d(c) has to be interpreted in a *narrow* or *broad* fashion.

To answer this question the OD relied on Article 5(1) (EPC Rule 23e(1)), which confirms that the human body at its various stages of formation and development cannot be patented. They reasoned that this rule prohibits the patenting of human embryos. Thus, if Rule 23d(c) was also intended to exclude only the patenting of human embryos it would be redundant over Rule 23e(1). Therefore, the rule must be intended to exclude something over and above just the human embryo. It was thus decided:

> In consequence, Rule 23d(c) EPC, in order to have a purpose exceeding the one of Rule 23e(1) has to be interpreted broadly to encompass not only the industrial or commercial use of the human embryos but also *human ES cells* retrieved therefrom by destruction of human embryos.

The outcome therefore was that human embryonic stem cells per se are not patentable under Rule 23d(c). This is in contradiction of the approach adopted by the UK Office.

Edinburgh University has appealed against this decision and the appeal remains pending. In the meantime there have been further developments in that two other cases are also pending the outcome of an appeal, both applications being refused at the examination stage without being granted. The results of these should have a bearing on the outcome in the Edinburgh case.

The WARF application

The first of these involves the pioneering work of Dr James Thomson at the University of Wisconsin, who first reported the isolation of human embryonic stem cells. The rights are assigned to the Wisconsin Alumni Research Foundation (WARF) which is the designated applicant for the application EP-A 0770125. The application was refused by the EPO Examining Division (ED) in July 2004, citing Article 53(a) EPC and Rule 23d(c) EPC as the reason for refusal.

The application sets out to secure a monopoly for a cell culture comprising

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primate embryonic stem cells which (i) are capable of proliferating *in vitro* for over one year, (ii) maintain a karyotype in which all chromosomes normally characteristic of the primate species are present and are not noticeably altered through culture for over one year, (iii) maintain the potential to differentiate to derivatives of endoderm, mesoderm and ectoderm tissues throughout the culture, and (iv) are prevented from differentiating when cultured on a fibroblast feeder layer. Although described in the application, its scope did not extend to methods of isolating stem cells from primate embryos, or to cells as they exist in the human body, but only cells in a culture produced by a technical process.

Objections of the examiner

The ED took the view that the provisions of Rule 23d(c) excluding from patentability 'uses of human embryos for industrial and commercial purposes' are not directed exclusively to the scope of the monopoly sought but rather *concern inventions*, thus excluding all aspects that make the subject matter available to the public.

Exclusion of inventions involving embryos

In the WARF case, since the application as filed did not provide any alternative starting material from which to prepare the cultured embryonic stem cells other than pre-implantation embryos, the cultured cells themselves were considered inseparable from the methods used to generate them and from the use of the embryo as a starting material. It was concluded that Rule 23d(c) excludes from patentability not only uses of human embryos but also any product that originates from human embryos whose isolation necessitates the *direct and unavoidable* use of a human embryo.

This decision went somewhat further than the Edinburgh case and raises the possibility that useful products isolated from cultured human embryonic stem cells might also not be patentable if their production is considered to ultimately require 'direct and unavoidable' use of an embryo.

The CIT application

The second case involves EP-A-0658194 in the name of California Institute of Technology. This application was refused by the Examining Division in October 2003, again citing Rule 23d(c).

The application covers a *method* of proliferating *in vitro* a cloned population of neural crest cells and does not seek patent protection for any method involving the step of recovering stem cells from an embryo. Nevertheless, the Examining Division again has applied a broad interpretation of the exclusion under Rule 23d(c) and has looked at what it considers to be the subject-matter of the application as a whole, rather than just the subject-matter that is explicitly sought to be covered by the applicant. In this case the application was refused notwithstanding that use of embryos was not unavoidable because the technique worked with adult cells as well.

Future developments

What these decisions seem to suggest for the first time is willingness for the EPO of itself to be a moral arbiter, without considering whether there is any consensus across the EPC contracting states concerning the morality of the technology per se. This, if followed, is significant departure from the previous practice.

However, the WARF case came before the Board of Appeal in November 2005. Following submissions from the Applicant, the Technical Board declined to rule on the matter but rather referred it to the highest EPO Authority, the Enlarged Board of Appeal, whose decision will be final. Unfortunately, the Enlarged Board tends to deliberate slowly so it could be several years before there is a final resolution of the matter.

In the meantime, EPO President Alain Pompidou has indicated that the EPO will, for the time being, stop making decisions on pending patent applications involving human embryonic stem cell technologies until the matter is finally decided, thus leaving a state of uncertainly

for applicants and the investment community.

OTHER TERRITORIES WITH DIFFICULTIES

Unlike Europe, most other territories do not include in their patent laws any exclusion to patenting on ethical grounds that are as broad as EPC Article 53(a). Nevertheless the potential remains for patent applicants in respect of stem cell technology to hit the buffers elsewhere. Canada is a case in point. Canadian Patent Statute does not provide moral exclusions but the Supreme Court has established a bar to the patentability of certain inventions, for example, higher animal life forms (see *Harvard College* v *Canada (Commissioner of Patents), 2002*).[4] It is also apparently accepted that 'human life' should not be patentable. Therefore, the Canadian Patent Office is currently deferring examination of patent applications that cover hES cells until it decides whether such applications are potentially directed to human beings bearing the cells in question.

Doubts in Canada

In Australia the law precludes the patenting of 'human beings and biological processes for their generation' and the Australian Patent Office interprets this to exclude foetuses, embryos and fertilised ova. It has been established by the courts that it is for parliament, not the courts or the Patent Office, to decide whether matters of ethics or social policy have any impact on what is patentable. Nevertheless, the Patent Office has adopted a policy whereby any patent application falling within a 'grey area' with respect to patentability must be referred to the supervising examiners, who will discuss the matter with the deputy Commissioner. It is understood that inventions involving hES cells are currently covered by this policy.

Issues in Australia

Japan is yet another territory that does not encompass broad statutory exclusions based on ethical considerations and a number of patents have been granted. However, in respect of stem cell technology the biggest hurdle relates to meeting the utility requirement since methods of isolation and use of stem cells must be industrially applicable. To the extent that the stem cells are being produced with a view to returning the cells to the human body, patents may be refused since inventions which are methods of medical treatment are not patentable.

THE USA

No discussion on stem cell patenting would be complete without considering the USA, probably the most liberal jurisdiction in the world where patentable subject matter is concerned. 35 USC 101 defines the criteria for patentability in the USA and states that:

> Whosoever invents or discovers any new and useful process, medicine, manufacture or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions or requirements of this title.

Of course, the 'conditions and requirements' are the usual ones for patent systems, novelty, non-obviousness, utility and an enabling disclosure. There is no specific bar in 35 USC against the patenting of inventions that might be considered immoral or unethical, although the US Patent and Trade Mark Office (USPTO) has a current practice of refusing to grant patents having a human being within its scope. However, it is not easily determined what inventions should actually be regarded as falling within this exclusion. The guiding principle in the US is that espoused by the Supreme Court in *Diamond* v *Chakrabarty*[5] that US patents should be granted for 'everything under the sun that is made by man'. It is not surprising, therefore, that the USPTO has been liberal in granting patents for stem cell technology.

This is not to say that controversy is very far from the surface. Two of the patents that have been granted are to WARF in respect of the Thompson work. Broadly, they cover human and

WARF dominate in US

other primate ES cell cultures and are equivalent to EP-A-0770125 discussed above. Of themselves, these patents give WARF considerable power over the development of hES cell therapies in the USA, since third parties will, by and large, require a licence from WARF to create their own hES cell lines. Of course, this is a situation that is not at all unusual for a pioneering technology. The inventors and their assignees quite often have control over its exploitation for a limited period via patent rights. Part of the role of patents is to encourage this type of innovation.

Ban on federally-funded research

It appears, however, that the control exercised by WARF may have become distorted in this case by the ban in 2001 on the generation of any new hES lines in the conduct of federally funded research.[6] At the time of the ban there were 22 hES cell lines 'eligible' for federal funding that were listed on the National Institutes of Health's (NIH) Human Embryonic Stem Cell Registry. To obtain these, potential buyers are channelled by the NIH to certain vendors, prominent among which is WiCell Research Institute, a non-profit subsidiary of WARF which manages transactions in the cell lines covered by the WARF patents. Licences accompany any sale by WiCell which define constraints on their use depending on whether the licenced use is scientific or commercial. This arrangement has been highly criticised on the basis that US tax dollars appear, at least, to be funding basic research for the exclusive commercial benefit of WARF. If overall control is exercised by WARF on stem cell research in the USA, then given the projected multibillion dollar regenerative medicine market, it seems litigation under these patents and attempts to render then invalid may not be very far away.

Litigation may not be far away

CONCLUSION

As with many important developments in biotechnology, the patenting of stem cell technology has proved as controversial as the technology itself. Europe has by far the broadest statutory exclusion against the patenting of inventions that might be considered unethical, as well as a very transparent patent system. The EPO has therefore experienced public objection of this type before and has been willing to allow patents for controversial technologies. Its recent position with respect to stem cells is at odds with the way it has previously dealt with these matters and suggests there may be political pressures upon it. An about turn is still possible, although a final decision is likely to take some years to be reached. Notwithstanding the lack of statutory reasons for refusing patents on ethical grounds, elsewhere patents are not being granted at the rate one would expect. Clearly, this is not a desirable situation if money is to be made available to realise the medical benefits of stem cell technology. The sooner all these doubts are resolved, the better. The controversy over the WARF stem cell patents in the USA represents the other side of the coin. The patent holders are regarded as too powerful. Given the amount of non-federal money being made available for stem cell research in the USA, these concerns may well be an illusion. Experience tells us that on balance the granting of patents encourages innovation and investment rather than hinders it.

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