The Limits of Patentability: Stem Cells

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Abstract This chapter discusses the status quo in the patentability of human embryonic stem cells in Europe and the United States. Further, alternative technologies will be considered with respect to practicability and patentability.

Keywords Stem cells · Patentability · Embryonic · WARF · Brüstle

1 Introduction

According to recent reports, the market for stem cell technologies will grow quickly within the near future. Although projected figures are subjected to significant variances (business information provider Visiongain Ltd (2012) predicts that the overall world market for stem cell technologies in medicine will reach $7.3 billion in 2014, while competitor Kalorma Information is more conservative, yet its estimate still predicts that the global market for stem cell technologies will rise over $700 million in 2012, and given some positive trends could reach over 1 billion dollars in the same year.

Practising stem cell related technologies, particularly the derivation thereof, is subject to a strong regulation in most developed countries. Large differences apply from country to country, e.g., whether the importation of hES cell lines or their derivation within a country is legal. To make it more complicated, some countries have even intranational differences. In the United States, for example, particular

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aspects of practising stem cell related methods are subject to state law, with large differences from state to state (Caulfield et al. 2009).

In any case, stem cell related technologies comes at the expense of tremendous costs, which makes meaningful patent protection an important condition for investors to decide whether they may want to spend money into stem cell R&D.

However, the patentability of stem cells, particularly of human embryonic stem cells (hES cells), is an issue which has been discussed both in the public as well as in the biopatent community in all major industrialized countries. Key aspects of the discussion circle around ethical concerns related to the respective technologies and to the monopolization and commercial use of such cells, and the therapeutical promises made by these approaches. The following article will give an overview of the actual state of the patent debate, and the recent case law, with respect to Europe, and the United States.

2 The Legal Framework for Patentability of hES Cells

Stem cell related technologies do, without doubt, raise new ethic questions on which most societies have no consensual answers yet. However, in their helplessness, societies tend to seek answers on these questions in the Patent Law. As a result, the number of special regulations which, for example, the European Patent Convention provides for biotechnology inventions exceeds those for any other technical discipline.

In all discussions related to ethical issues of stem cell patents it should, however, be kept in mind that a patent is not a right to practice, but an exclusive right, i.e., a right to exclude others from practising an invention. The right to practice is dependent on (a) the respective legislation[1] and (b) existing patents of third parties. In case, a society may want to ban particular types of inventions which are deemed to be ethically problematic from being put into practice, the exclusion thereof from patent protection is, thus, an unsuitable tool.

2.1 Europe

As set forth in the European patent convention (EPC) and in the German Patent Act (PatG), patents are being granted for inventions, which are novel, rely on an inventive step and are industrially applicable. Both legal frameworks comprise generic clauses according to which inventions the commercial exploitation of which would be contrary to ordre public or morality are exempt from patent protection (Art 53 a) EPC, §2 (1) PatG). However, such exploitation shall not be

[1] In Germany, the derivation and use of hES cells is regulated by the German Stem Cell Act, while the use of embryos is regulated by the German Act on the Protection of Embryos.

deemed to fall under this exemption only because it is prohibited by law or regulation in some or all of the Contracting States. Accordingly, the Courts in the EU member states and the Technical Boards of Appeal of the European patent office (EPO) have rarely made use of said general clause.

In all cases, the question whether a given technology falls under this exemption requires a careful weighing up of the invention's usefulness to mankind against severity of the violation of *ordre public*. Cases where a given technology was considered to fall under this exemption encompass a coffin which could be evacuated to exclude that a seemingly dead wakes up after being buried,[2] and some biotechnological inventions in particular, e.g., a transgenic animal having increased probability of developing cancer.[3] Such mammal was claimed to be useful for cancer research, but since it could not be assumed that the only examples in the application, namely mice, could be extended to other animals, the Board of Appeal required that the claims are restricted to mice, because the patent would otherwise protect methods applied to animals other than mice (e.g., beavers), where the suffering involved would not be justified by sufficient benefit for mankind.

In Europe, biotechnological inventions are subject to European Directive 98/44/EG ("Biopatent Directive") since July 1998. The directive has subsequently been implemented into the respective laws of the EU member states as *lex specialis* over the generic exclusions as to "*ordre public*" discussed above.

Furthermore, the EPO has also implemented those clauses provided in the Regulation which refer to questions of patentability, although the EPO is not a body of the European Union, and was thus not obliged to do so. Interestingly, this means that regulations issued by the European Union became applicable law to non-EU states, as for example Switzerland, Turkey of Norway.

The key regulations set forth by the Biopatent Directive with respect to stem cells are as follows:

2.1.1 Positive Definition

A a positive definition, Art. 5 (2) sets forth that an element isolated from the human body may constitute a patentable invention, even if the structure of that element is identical to that of a natural element. This provision is commonly seen as the basis for the patentability of cells as such, including human cells.

2.1.2 Exclusions from Patentability

However, according to Art. 5 (1), the human body at the various stages of its formation and development cannot constitute patentable inventions. According to

[2] Decision of the German Patent Court, BPatG 23 W (pat) 248/70.

[3] EPO technical Board decision T 0315/03 (Transgenic animals/HARVARD).

Table 1 Overview of stem cell related clauses in the Biopatent Directive 98/44/EG

Directive 98/44/EG	Legal text	Implementation into the EPC
Art 5(1)	The human body at the various stages of its formation and development […] cannot constitute patentable inventions	Rule 29 (1)
Art 5(2)	An element isolated from the human body […] may constitute a patentable invention, even if the structure of that element is identical to that of a natural element	Rule 29 (2)
Art 6	Inventions shall be considered unpatentable where their commercial exploitation would be inconsistent to public policy or morality. The following, in particular, shall be considered unpatentable:	Art 53 a
	(a) methods for cloning human beings	Rule 28 (a)
	(c) the use of human embryos for industrial or commercial purposes	Rule 28 (c)

Art. 6, inventions shall be considered unpatentable where their commercial exploitation would be inconsistent to public policy or morality. In particular, Art. 6 sets forth that methods for cloning human beings (Art. 6(a)), and the use of human embryos for industrial or commercial purposes (Art. 6(c)) shall be considered unpatentable.

It is important to mention that, furthermore, Art. 6 sets forth that the said commercial exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation. This means that particular indications supporting the *ordre public* issue are necessary to expel an invention from patentability. It is, however, common understanding that the examples mentioned in Art. 6 (particularly examples (a) and (c)) qualify as violating *ordre public* (see Table 1).

2.2 The United States

Compared with the extremely regulated situation in Europe, Title 35 of the United States Code has no specific exemptions for stem cell related patents. 35 U.S.C. §101 reads as follows:

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

Obviously, 35 U.S.C. §101 mentions four categories of patentable subject matter, namely (any new and useful) process, machine, manufacture, or composition of matter. This list has long been interpreted as containing an implicit exception related to laws of nature, natural phenomena, and abstract ideas, which for a long time were deemed not patentable even by the US Supreme Court.[4]

[4] O'Reilly v. Morse, 56 U.S. 62 (1853).

Later on, the Courts recognized that too broad an interpretation of this exclusionary principle could eviscerate patent law. In *Diehr*[5] the Supreme Court pointed out that "a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm, and that an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." This increasingly liberal position culminated in Supreme Court decision *Diamond v. Chakrabarty,*[6] which issued in 1980, and according to which, as the Court put it, "Congress intended statutory subject matter to 'include anything under the sun that is made by man'".

Thus, no statutory exemptions from patentable subject matter exist for stem cell related inventions in the United States. Further, 35 U.S.C. §101 has no general exclusions as to "*ordre public*". Purified and isolated stem cells and human cloning-related inventions are thus considered patentable subject matter in the United States.

Recently, the Supreme Court has again restricted this very broad concept. In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*[7] a patent application related to a method of optimizing therapeutic efficacy for treatment of an immune-mediated disorder was deemed unpatentable because it was held that the claims effectively related to the underlying laws of nature themselves only. It is so far difficult to predict whether this decision will affect the patentability of hES cells. The decision is discussed in further detail below.

3 Case Law

3.1 Europe

The Biopatent Directive fails to properly define, among others, the term "embryo" and "human body". Some key issues related with the patenting of stem cell related inventions were thus unclear for a couple of years. These were, among others, the following:

(a) Does a given stem cell process involve the use of human embryos for industrial or commercial purposes ?
(b) Can a given stem cell as such be considered as being an embryo ?
(c) Can a given stem cell be considered as a human body at a stage of formation ?

These questions were addressed by the highest European authorities in Biopatent law, namely the Enlarged Board of Appeal (EBA) of the EPO and the European Court of Justice (ECJ). The two respective cases will be discussed in the following:

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[5] Diamond v. Diehr, 450 U.S. 175 (1981).

[6] Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980).

[7] Mayo Collaborative Servs. v. Prometheus Labs., Inc., 130 S. Ct. 3543 (2010).

3.1.1 The WARF Decision

In 2006, the EBA issued the so-called WARF decision.[8] The patent application in dispute (EP770125, inventor: James Thomson) was assigned to the Wisconsin Alumni Research Foundation (WARF). Its US counterpart has been nicknamed as "bottleneck patent" for all commercial stem cell products (Bergman and Graff 2007) due to its broad scope. The main claim of EP770125 was as follows:

A purified preparation of primate embryonic stem cells which

(a) is capable of proliferation in vitro culture for over 1 year,
(b) maintains a normal karyotype through prolonged culture,
(c) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and
(d) will not differentiate when cultured on a fibroblast feeder layer.

The EBA has rejected the application due to a violation of Rule 28 (c) EPC, i.e., because it considered that the claimed embryonic stem cells involved, at least at the time of filing, the use of a blastocyst, which the EBA considered as an embryo. As the term "primate" encompasses "human", the EBA found that the criterion according to which a use of human embryos for industrial or commercial purposes is excluded from patentability was met.

The fact that the use of human embryos was not explicitly recited in the claims was deemed irrelevant, as the EBA considered the whole disclosure, not only the claims. Furthermore, the EBA stated that at the time of filing the cell cultures claimed could only be obtained by the blastocyst approach, which means that it required the destruction of human embryos.

The keynotes of the decision were as follows:

2. Rule 28(c) EPC forbids the patenting of claims directed to products which---as described in the application---at the filing date could be prepared exclusively by a method which necessarily involved the destruction of the human embryos from which the said products are derived, even if the said method is not pArt. of the claims.

4. it is not of relevance that after the filing date the same products could be obtained without having to recur to a method necessarily involving the destruction of human embryos.

The decision has often been interpreted as leaving room for patent applications related to the production of stem cells, or stem cells as such, if such application

[8] Decision G2/08.

describes at least one alternative way to produce the said cells (i.e., not related to, or involving, hES cells).

3.1.2 The Brüstle Case

Another case related to the patentability of hES cells has recently been decided by the ECJ. The case related to the German patent assigned to Professor Oliver Brüstle, who is a researcher at Bonn University, Germany. The patent was related to neural progenitor cells which have been derived from hES cells legally obtained under the deadline solution provided by the German Stem Cell Act (StZG).

In contrast to the WARF patent, this patent did, therefore, not relate to hES cells as such. While hES cells were disclosed as preferred source for the claimed neural progeny cells, cells obtained by parthenogenesis and cells obtained after somatic nuclear cell transfer were mentioned as alternative sources (although it seems to be arguable if they represent a technically feasible alternative).

Foreplay Under German Jurisprudence

The patent was granted in 1997 with the following main claim:

> Isolated, purified progenitor cells with neuronal or glial properties of embryonic stem cells, comprising a maximum of 15 % primitive embryonal and non-neuronal cells, which are obtained by the following steps:
>
> (a) cultivation of ES-cells to obtain embryoid bodies,
> (b) cultivation of embryoid bodies to obtain neuronal progenitor cells
> (c) [...]

In 2004, Greenpeace filed a nullity suit against the patent, in the course of which the Federal Patent Court (BPatG) declared the patent invalid due to violation of § 2 (2) Nr. 3 PatG (which corresponds to Art. 6c Biopatent Directive) in 2006. The applicant went into appeal before the Federal Supreme Court (BGH).

Of course, the BGH has to apply German law and, as such, the EU Biopatent Directive when reexamining German patents. This means that in questions related to the patentability of German Biotech patents, the ECJ is the final instance for the interpretation of the respective rules.

For these reasons, the BGH decided on 12 November 2009 to stay proceedings and submit a referral to the ECJ for an interpretation of the Biopatent Directive, particularly of the terms "embryo" and "industrial"/"commercial".[9]

[9] BGH "Neurale Vorläuferzellen", Akz: Xa ZR 58/07.

In his referral, the BGH addressed different issues. First of all, the BGH wanted to know whether or not hES cells, cells obtained by somatic nuclear transfer, cells obtained by parthenogenesis and/or induced pluripotent cells (iPS) qualify as embryos (Art. 6) or as a human body at a stage of its formation and development (Art. 5).

Next, the BGH asked if cells which have been obtained directly or indirectly from hES cells are excluded from patentability (Art. 6) because, for the latter, an embryo was destroyed ("Fruits of the forbidden tree")?

The BGH, furthermore, noted that the research of Prof. Brüstle was publically funded and has, thus, been considered, at least once, to be in line with *ordre public*. It would thus be surprising, the BGH suggested, if same did not apply for resulting patent applications.

In addition, the BGH suggested, in his referral, that the term "embryo" should be defined according to § 8 of the German Act for the Protection of Embryos (EschG), which requires totipotency. This would mean that hES cells, which are not totipotent, do not qualify as embryos. However, the Act for the Protection of Embryos is a German law which is not an implementation of a European Directive, which means that the ECJ is not bound to said definition, and the BGH could only suggest to adopt the latter.

The Decision Issued by the European Court of Justice

In cases which raise a new point of law, decisions by the European Court of Justice are anticipated by an opinion issued by one Advocate General. Hence, as under the Biopatent directive, only one case had made it to the ECJ yet at that time,[10] which however was not related to hEScell issues, the Advocate General came again into play. On March 10, 2011, Advocate General M. Yves Bot recommended to answer the questions referred to the ECJ by the BGH with respect to Article 6(2)(c) of Directive 98/44/EC in that

- the concept of a human embryo applies from the fertilization stage to the initial totipotent cells and to the entire ensuing process of the development and formation of the human body, which includes the blastocyst;
- unfertilized ova into which a cell nucleus from a mature human cell has been transplanted or whose division and further development have been stimulated by parthenogenesis are also included in the concept of a human embryo in so far as the use of such techniques would result in totipotent cells being obtained;
- pluripotent embryonic stem cells are not included in that concept because they do not in themselves have the capacity to develop into a human being;
- an invention must be excluded from patentability where the application of the technical process for which the patent is filed necessitates the prior destruction

[10] Monsanto vs. Cefetra, C-428/08.

of human embryos or their use as base material, even if the description of that process does not contain any reference to the use of human embryos; and
- the exception to the non-patentability of uses of human embryos for industrial or commercial purposes concerns only inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it.

The ECJ's decision issued 18 October 2011.[11] Not surprisingly, the ECJ essentially agreed with the Advocate General's opinion, and concluded that (i) any human oocyte after fertilization, (ii) a non-fertilized human oocyte into which a cell nucleus from a mature human cell has been transplanted, and (iii) any non-fertilized human oocyte the division and further development of which have been stimulated by parthenogenesis constitute a human embryo, and are thus excluded from patentability.

Further, the ECJ found that an invention is also excluded from patentability if the technical teaching requires prior destruction of a human embryo, or its use as base material, whatever the stage at which that destruction occurs, and even if said destruction is not part of the claimed technical teaching and does not refer to the use of human embryos.

The ECJ, furthermore, found that the exclusion from patentability concerning the use of human embryos for industrial or commercial purposes, as set out in Article 6(2) (c) of Directive 98/44/EC, also covers the use of human embryos for purposes of scientific research, because the grant of a patent already implies, in principle, its industrial or commercial application.

Still, patentability of inventions using human embryos is patentable for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it. However, it remains unclear what exactly is meant by the "use of a human embryo for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it".

With respect to pluripotent stem cells obtained from hES cells—which are not covered by the definition of "human embryo" as set forth by the ECJ because they do not qualify as totipotent—the ECJ ruled that it is for the referring Court to ascertain, in the light of scientific developments, whether such cells are capable of commencing the process of development of a human being and, therefore, are included within the concept of "human embryo" within the meaning and for the purposes of the application of Article 6(2)(c) of Directive of the Directive. Please note that these pluripotent cells are not to be confused with "induced pluripotent stem cells" (iPS cells), which are discussed herein below, and which have not been addressed by the ECJ.

[11] Oliver Brüstle vs. Greenpeace eV, C-34/10.

3.1.3 Differences Between Both Decisions

Interestingly, the ECJ's understanding of the term "human embryo" is consistent with that the EBA gave in the WARF decision. However, while the WARF decision has often been interpreted in such way that (i) patent applications which relate to inventions made after the underlying hES cell lines became available, and (ii) patent applications related to the production of stem cells, or stem cells as such, which describe at least one alternative way to produce the said cells (i.e., not related to, or involving, hES cells), are both patentable, such bypass is no longer possible in the understanding of the ECJ.

Although ECJ jurisdiction has no legal bearing for the granting practice of the EPO, the latter's president Benoît Battistelli announced in his Weblog,[12] on November 3, 2011, that "if the judges rule in favour of a restrictive interpretation of biotech patentability provisions, the EPO will immediately implement it". If any difference between the positions of the EPO and the ECJ has existed before, the EPO has thereby deliberately surrendered their position in favor of that of the ECJ.

As a result of the ECJ Decision, it is to be expected that the BGH will confirm the Germen Federal Court of Justice's declaration of invalidity of at least claims 1, 12, and 16 of German Patent No. 197 56 864.

3.1.4 Reactions by the Biotech Community

While the exemption from patentability does, as such, not affect the use of hES cells, it will affect the protection of research results, and thus may hamper the commercial exploitation of products and methods involving hES cells, and, hence, R&D related to hES cell-based therapies.

Not surprisingly, the Biotech community has reacted on the ECJ decision with intense indignation. In Germany alone, ten major research organizations, including the German Research Foundation (DFG), the University Rectors Conference and the Max Planck Society, published a joint statement in which they disapprove the decision, and polemize on its impact on stem cell research in Europe.

It will in fact be doubtable whether applied research on hES cells will still play a significant role in Europe. Sponsors will be hesitant to provide funds for applied research if it is already clear that the results of such research cannot be monopolized for a given period to recompensate the investments made. This means that applied research on hES cells will very likely decrease in Europe, thus turning Europe into a developing region at least with respect to this discipline.

Other voices state that the decision will not have any practical consequences, because it does not prohibit the respective stem cell related methods or products, but merely excludes the underlying inventions from patentability.

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[12] see http://blog.epo.org/uncategorized/patents-and-biotechnology-%E2%80%93-latest-developments/.

Because of the fact that in other major jurisdictions these limitations do not exist, so the argumentation (the US counterpart to the Brüstle patent, US 7,968,337, has been granted on June 28, 2011, i.e., about 4 months prior to the ECJ's decision and after the opinion of the Advocate General issued) a lack of protection in Europe alone would not be enough incentive for imitators to develop a counterfeit product exclusively for the European market. This amazingly calm position has been criticized as being mere calculated optimism in order to mollify investors, others say.

3.2 The United States

Like elsewhere, ethic questions are an evergreen issue in the history of stem cells in the United States, too. However, as set forth above, 35 U.S.C. §101 has no general exclusions as to *ordre public*, and no statutory exemptions from patentable subject matter exist for stem cell related inventions in the United States.

Only the Manual of Patent Examining Procedure (MPEP), which contains guidelines for the examiners at the USPTO, has codified, in section 2105, a clause according to which "if the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. §101 must be made indicating that the claimed invention is directed to nonstatutory subject matter".

Further, the revision of the US Patent system in 2011 under the Leahy Smith Act, which came as quite a surprise, brought with it some significant changes. Among others, 35 U.S.C §101 will be amended by adding a passage according to which "no patent may issue on a claim directed to or encompassing a human organism."[13]

In an internal memorandum of September 20, 2011, the US Patent and Trademark Office (USPTO) informed its employees that this new clause merely codifies existing USPTO policy that human organism are not patent-eligible subject matter. It remains, however, to be seen, how the examiners put this clause into daily practice. Fears exist that stem cells, particularly hES cells, will sooner or later fall under this exemption as qualifying as a human organism.

3.2.1 Case Law with Respect to Patentability Issues

In two related cases concerning patent applications directed to a human/non-human chimera filed by Stuart Newman and Jeremy Rifkin, the USPTO rejected the both applications. In the first case[14] the USPTO emphasized that the

[13] Section 33(a) of the Leahy-Smith America Invents Act.

[14] US patent application No 08/993,563 filed by Stuart Newman and Jeremy Rifkin.

application would violate the utility requirement set forth in 35 U.S.C. §101, in that "inventions directed to human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement." The inventors refiled their application at a later stage, wit the same result. This time, the USPTO argued that although 35 U.S.C. §101 did not explicitly exclude the patentability of humans, the USPTO's position of rejecting such patent applications was implicitly encompassed by said statute.

The USPTO bypassed the Supreme Court's ruling in *Diamond v. Chakrabarty* by postulating that Congress could not have intended humans to be included as subject matter under 35 U.S.C. §101. This postulation resulted from an interpretation of the 13th Amendment of the US constitution, which abolishes slavery. Similarly, in *Tol-O-Matic Inc. v. Proma*[15] the USPTO stated that the utility requirement of 35 U.S.C. §101 excludes inventions deemed to be injurious to the well being, good policy, or good morals of society.

However, these decisions have not affected the general granting practice of the USPTO related to stem cells, which are granted by the USPTO on a regular basis (Bergman and Graff 2007). The real battles are today fought on other grounds.

The WARF Cases

One of the first applicants that had created a meaningful IP portfolio protecting methods for the production of hES cells is Wisconsin Alumni Research Foundation (WARF). Other players are Geron of Menlo Park, CA, and the NIH, who all stand in contractual relationships to one another, and have thus been nicknamed "gatekeepers of hES cell products" by some authors (Rabin 2005).

On July 17, 2006, Jeanne Loring, then associate professor at the Burnham Institute for Medical Research, Dan Ravicher, an attorney who had founded the Public Patent Foundation, and John Simpson of the Foundation for Taxpayer and Consumer Rights filed a request for re-examination of three WARF patents granted for methods related to the production of Primate Embryonic Stem Cells, namely US 5,843,780, US 6,200,806, and US 7,029,913, on the grounds of obviousness in view of published prior art.

On March 30, 2007, the USPTO rejected all three patents in their entirety on the grounds of obviousness. These decisions were appealed by WARF, with the result that US 5,843,780 and US 6,200,806 were upheld in amended form in March 2006, while the revocation of US 7,029,913 was confirmed on April 28, 2010, by the USPTO board of Appeals,

[15] Tol-O-Matic Inc. v. Proma Produkt-und Marketing Gesellschaft, 945 F.2d 1546 (Fed Cir 1991).

The Prometheus and BRCA Cases

Two other Court cases may have unprecedented effects on the patentability of stem cells, too.

In *Mayo Collaborative Services v. Prometheus Laboratories*,[16] the US Supreme Court overturned a prior decision by the Court of Appeals of the Federal Circuit, by judging that a method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, as claimed in US Patent US6, 680, 302 assigned to Prometheus Laboratories, do not meet the patentable subject matter standard of 35 U.S.C. 101.

The claimed method comprised administering a given drug to a subject and determining its level, or of a metabolite thereof, in said patient, wherein a level below of a given threshold indicates to increase the dose of said drug and a level above the threshold indicates to decrease the dose thereof.

The Supreme Court considered that "the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." For these reasons, the Court considered "that the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." Accordingly, the Court asked whether "the patent claims add enough to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?"

The Court concluded that this is not the case, because "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." Thus, the Court held the claims invalid for claiming natural laws, which as the Court put it, are not patentable subject matter under 35 U.S.C. 101, thus reviving a long-forgotten position, namely that, due to the fact that 35 U.S.C. 101 mentions only process, machine, manufacture, or composition of matter, laws of nature are implicitly excluded.

In *Association for Molecular Pathology vs. USPTO*,[17] a consortium of plaintiffs challenged couple of patents assigned to Myriad Genetics, namely US 5,747,282, US 5,837,492, US 5,693,473, US 5,709,999, US 5,710,001, US 5,753,441, and US 5,753,441. Next to the USPTO, Myriad acted as a defendant.

The plaintiffs claimed that 15 claims from these seven patents assigned to Myriad were drawn to patent-ineligible subject matter under 35 U.S.C. §101. The District Court of Southern New York revoked the patents in March 29, 2012, stating that they were directed to a law of nature.

In the subsequent appeal proceedings before the Court of Appeals of the Federal Circuit, the Department of Justice (DOJ), interfered and argued for the

[16] See footnote 7.

[17] Association for Molecular Pathology v. Myriad Genetics, Inc. No. 10-1406 (Fed. Cir. 2011).

plaintiffs, i.e., against the USPTO. DOJ's federal attorneys suggested what has become notorious as the "magic microscope", according to which (i) a magic microscope can look deep inside cells and find any natural molecule in them, and (ii) any natural molecules that it can find should be excluded from patent protection, since "products of nature" have never been patentable.

Judge Moore, who was a member of the CAFC panel of judges, referred to the magic microscope test as "kitschy". Eventually, in a 2–1 decision the Court revoked the first instance decision, stating, among others, that (1) isolated genes, cDNAs and partial isolated gene sequences are patentable subject matter under §101 as well as (2) methods of screening potential cancer therapeutics by analyzing growth rates of cells with altered BRCA genes in the presence or absence of the treatments. Claims to methods of analyzing BRCA gene sequences and comparing those with cancer-predisposing mutations to normal or wild-type gene sequences were held not to be directed to patentable subject matter.

Not surprisingly, both parties filed a petition seeking rehearing. Eventually, the case was carried to the Supreme Court, who on March 26, 2012 remanded it back to the CAFC for further consideration in light of Mayo Collaborative Services v. Prometheus Laboratories. The latter has, on August 16, 2012, affirmed that isolated human genes are patent-eligible subject matter. The Court emphasized that the Supreme Court's recent decision in Mayo Collaborative Services v. Prometheus Laboratories was not decisive for the instant case, though the Supreme Court's analysis was considered "nonetheless instructive".

However, although they do not relate to stem cells, both cases cast new doubts on the future of hES cell patents, at least in the USA. Notwithstanding this, patent applications related to hEScells are steadily filed, and granted, in the United States

3.3 Non-Patent Related Battlefields

However, patent disputes are only one side of the medal in the USA. Another battle was, and still is, fought namely on the side of public financing. According to the "Dickey Wicker amendment", which was a appropriation bill rider attached to a bill passed by United States Congress during the Clinton administration, the Department of Health and Human Services (HHS) was banned from using public funds for the creation of human embryos for research purposes, or for research in which human embryos were destroyed. Under the Bush administration, the federal financing of research devoted to embryonic stem cells was restricted to 21 already existing cell lines, in order to discourage the use of new embryos for the generation of new stem cell lines. President Obama promised in his electoral campaign to lift these restrictions, in order to expand the number of hES cell lines eligible for federally funded research. In an executive order of March 9, 2009, he instructed the NIH to remove existing limitations on scientific inquiry, and to expand NIH support for the exploration of human stem cell research.

Shortly thereafter, the NIH published draft guidelines allowing funding for research on stem cells derived from donated embryos leftover from fertility treatments. Further, NIH would continue to fund research on adult stem cells and induced pluripotent stem cells. Research on embryos created specifically for research or on stem cells derived by research cloning techniques or by parthenogenesis would not be supported.

A large public discussion followed. In the final guidelines, which took effect July 7, 2009, it was set forth that previously derived stem cell lines that follow the spirit of the new ethical guidelines would be eligible for funding. Further an NIH advisory panel would evaluate these older stem cell lines if needed.

On August 19, 2009, the NIH was sued by two researchers, James L. Sherley, an adult stem cell researcher at the Boston Biomedical Research Institute, and Theresa Deisher, R&D director at AVM Biotechnology in Seattle, before the Federal District Court in Washington.[18]

The claimants, who were backed, among others, by Christian organizations, contended that the funding of embryonic stem cell research would unfairly divert money from adult stem cell research.

As a result, Judge Lamberth issued a preliminary injunction on August 23, 2010, banning federal spending on human embryonic research. The US Government quickly filed an appeal, but in the meantime the NIH had already shut down part of their hES cell research, and stayed grants to researchers that had not yet been paid out. On September 9, 2010 the Appeals Court for the DC Circuit allowed the request to stay the injunction, and the NIH could resume its hES cell programs.

On September 27, 2010, the Appeals Court ruled that the federal funding could go on while the appeals process moved forward, and on April 29, 2011 blocked the decision in a 2–1 ruling, and remanded it back to the District Court. Notably, the dissenter of said decision Judge Lecraft Henderson said her colleagues had performed "linguistic jujitsu". Following this prejudice, Judge Lamberth dismissed the lawsuit on July 27, 2011, thus paving the way for federal funding of hES cell related research. For 2011, the NIH allotted $358 million for non-embryonic stem cell research, and $126 million for embryonic stem cell research.

On August 24, 2012, the Appeals Court for the DC circuit eventually confirmed this decision. Judge Sentelle stated that the Dickey-Wicker act permits federal funding of research projects that utilize already-derived embryonic stem cells, which the court considered are not themselves embryos, because no "human embryo or embryos are destroyed" in such projects.

Thus, the court came at least in one aspect to the same finding as the ECJ and the EBA—namely that embryonic stem cells are not embryos as such.

[18] Sherley et al. vs NIH, 1:09-CV-1575.

4 Digressions

4.1 The European Side Battle

As already indicated above, the EPO and the EU are different bodies, and the legal system created under the European Patent Convention (EPC) is generally independent from EU legislation. In order to increase its influence in the patent domain, the EU has however tried to issue directives related to patent matters, which would then become applicable law in the EU member states.

So far, the EU has only managed to issue a directive related to Biotech Inventions (Biopatent Directive 98/44/EG), while an approach to issue a directive related to software patents[19] was dismissed by the European Parliament in 2005.

Through said backdoor, however, the ECJ became the highest instance for issues related to the enforcement of European Biopatents, and for questions related to the validity of national Biopatents, including Biopatents issued through the EPO pathway, too. In all cases the patent-unfriendly attitude and the lack of legal expertise at the ECJ is alarming.

The outcome of the recent Monsanto/Cefetra case,[20] in which the ECJ has dramatically compromised the concept of compound protection, has already confirmed the author's fears related to ECJ's expertise and attitude with respect to patents, particularly to Biopatents (Hüttermann and Storz 2010).

One issue discussed peripherally in the "WARF" case related to the question whether or not the EBA should submit a referral to the European Court of Justice (ECJ) for its opinion on the case. The EBA denied this initiative because (i) neither EPC nor European Law provide a pathway under which EBA can actually send a referral to the ECJ, and (ii) ECJ ruling has no legal effect on the EPO.

On June 15, 2012, a coalition of Patient associations and leading research funders called on the European Parliament to continue EU funding for embryonic stem cell research. The latter is currently debating "Horizon 2020", which is the EU's program for research and innovation for the years 2014–2020. Some provisions in the draft regulation relate to the funding of stem cell research, which is still possible under the current Framework Programme 7. However, these provisions are challenged by delegates who believe that public funds should no longer be spent on embryonic stem cell research.

[19] Proposal COM/2002/92/FINAL.

[20] Case C-428/08.

4.2 ECJ and TRIPS

The TRIPS[21] contract is a contract related to the mutual acceptance of IP rights which has been signed by all WTO member states. In TRIPS, the WTO member states have agreed that they will accept particular standards related to patentability, and that patents shall be available for any inventions, whether products or processes, in all fields of technology Art 27 (1). In Art. 27 (2), TRIPS provides the option that member states may exclude from patentability inventions the commercial exploitation of which is may affect protect *ordre public* or morality.

The EU is not a member state of the WTO, but has ratified TRIPS. According to the ECJ, TRIPS has no direct effect on EU legislation. However, the recitals of the Biopatent Directive indicate that TRIPS was taken into account when the directive was drafted.

Should the ECJ exclude hES cells from patentability, this would probably be in line with Art 27 TRIPS, because the *ordre public* issue seems to be a real issue in the member states. However, it is quite unclear if iPS cells and other cells would satisfy this criterion, too.

4.3 When is an Embryo an Embryo?

In his judgement in the Brüstle case, the ECJ decided that "any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted, and any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis constitute a 'human embryo'" in the meaning of the Biopatent directive;

It is, however, interesting how the ECJ comes to this solution. The approach seems to be a mere teleological approach, because the ECJ does not relate to legal definitions in the different EU member states, but merely constitutes that "Recital 38 in the preamble to the Directive states that the list" of inventions mentioned in the Directive as being contrary to *ordre public* "is not exhaustive, and that all processes the use of which offends against human dignity are also excluded from patentability". Further, the ECJ argues that the "context and aim of the Directive thus show that the European Union legislature intended to exclude any possibility of patentability where respect for human dignity could thereby be affected". The Court thus concludes "that the concept of 'human embryo' within the meaning of Article 6(2)(c) of the Directive must be understood in a wide sense." The ECJ thus defines the term "human embryo" entirely de novo.

EU member states have, however, already defined the term "human embryo" in the past. The German Act for the Protection of Embryos, for example, defines the term under § 8 (1) as a "fertilized, viable human ovum from the beginning of

[21] TRIPS is an acronym for "Trade Related Aspects of Intellectual Property Rights".

nuclear fusion, plus totipotent cells extracted from an embryo which can divide under appropriate conditions and develop into an individuum".

Some legal systems see a major cesura 14 days after fertilization. Before this point, the embryo can still be split to develop into two or more children. Further, the embryo has no primitive streak, which is considered as the first step in the development of a central nervous system before that date. This situation has been declared equivalent to a situation in which a patient which has been diagnosed as brain dead and is declared eligible as an organ donor.

This concept is, for example, reflected in the UK Human Fertilisation and Embryology Act 1990, which in section 3 prohibits keeping or using an embryo after the appearance of the primitive streak (Sect. 3a), which is taken to have appeared in an embryo not later than the end of the period of 14 days beginning after fertilization. Dr. Brüstle has used this argument in his ECJ case to define the meaning of the term "embryo" as used in the Biopatent Directive—to no avail, as we all know now.

Interestingly, the Jewish understanding of an embryo which requires utmost protection is completely different. It seems that the Jewish tradition attributes minimal life value to early-stage embryos outside the female uterus. The Talmud defines any embryo up to 40 days old as a mere fluid. Further, it seems also important whether the embryo is inside a woman's uterus or in a lab, where it cannot develop into a child. According to even conservative Rabbis it is thus considered a "*mitzvah*", i.e., a religious mandate, to use those embryos for the benefit of society.

5 Alternatives to hES Cells

In the following, alternatives to hES cells and their potential to avoid the ethical problems raised by hES cells will be discussed. Further, it will be discussed whether these alternatives are, or will be deemed as, patentable subject matter in light of the above decisions. See Table 3 for a summary.

5.1 Cells Obtained by Somatic Cell Nuclear Transfer

This method involves the production of a blastocyst, which was considered as an "embyro" by the EBA and the ECJ. The method further qualifies as a "cloning method", and is thus unpatentable if related to humans.

Before the Brüstle case, no explicit case law existed with respect to these cells, but the BGH referral addressed this issue, too, because the respective cells are mentioned in the Brüstle patent as alternatives to hES cells. As discussed above, the ECJ found this type of cells unpatentable, too. Interestingly, somatic cell

nuclear transfer (SCNT) patents granted by the EPO before the ECJ decision relate exclusively to methods or cells referring to non-human animals.[22]

5.2 Stem Cells Obtained by Parthenogenesis

Methods for the production of stem cells by means of parthenogenesis have been seen as a possible solution for the ethical dilemma raised by hES cells. However, the respective methods are still under R&D and not yet ready to be put into practice. The methods involve the production, and destruction, of a blastocyst which is diploid for its maternal genes. For this reason, however, the blastocyst cannot become a viable organism.

While the method is surely not a cloning method, it remained arguable whether or not said blastocyst qualifies as an "embryo", or as a "human body in a stage of formation". The BGH had addressed this issue in his referral, and the ECJ found this type of cells, like cells obtained by somatic cell nuclear transfer.

5.3 Induced Pluripotent Stem Cells

Like stem cells obtained by parthenogenesis, the reprograming of differentiated somatic cells has been seen as a possible solution for the ethical dilemma raised by hES cells. In fact, the reprograming approach avoids the use of human blastocysts, and creates pluripotent cells.

The UK patent office (UKIPO), which is also bound to the provisions of the Biopatent Directive (as the priority date of said application ranks later than the implementation of the Biopatent Directive into UK law)[23] has granted the first iPS-related patent outside of Japan by Jan 12, 2010 to iPierian, which is Bayer Schering affiliate. The patent (GB2450603) relates to an iPS method which involves the use of Klf-4, Oct-4 and Sox-2, but excludes use of c-Myc. The inventor is Kobe-based iPierian researcher Kazuhiro Sakurada.

The outcome of this case has no legal bearing on one parallel EP case (EP2171045), which is still pending, although *ordre public* issues have not been raised in the latter so far. The pending claims in this application require the use of Oct3/4, Sox2 and Klf-4 plus contacting the cells with histone deacetylase inhibitor (HDACi), unlike in the UK, in which the exclusion of c-Myc was sufficient, the applicant preferred to positively recite HDACi, which is discussed as a substitute the oncogene c-Myc in the pertinent literature.

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[22] According to a study performed by the author.

[23] In the UK, the Biopatent Directive applies to patents filed on or after July 28, 2000, while the priority date of the Sakurada application is June 15, 2007.

Table 2 Overlapping scopes of the EP patents of Shinya Yamanaka and Kazuhiro Sakurada

Yamanaka (Kyoto) EP1970446 B1 (granted)	Sakurada (Kobe) EP2171045 A1 (pending)
Oct and Klf and (Myc and/or cytokine), Sox optional	Oct and Klf and Sox plus HDACi

Interestingly, Shinya Yamanaka of Kyoto University, who pioneered iPS methods, has filed a patent application (EP1970446) which has an earlier filing date than the Sakurada patent. While the main claim as filed recited only Oct, Klf, and Myc, the latest examination report required to also recite Sox, as in a later Yamanaka publication all four factors were considered necessary.

On May 16, 2011, the EPO issued a communication of intention to grant a patent on this application The claims as accepted for grant relate to a nuclear reprograming factor which comprises an Oct gene/gene product, a Klf gene/gene product, plus either a Myc gene/gene product or a cytokine.

The acceptance came quite surprisingly, because initially, the EPO had objected the said claim under Arts 83 and 84 EPC (lack of clarity/lack of enablement), due to a prior publication by the inventor according to which the induction process could be accomplished only by treatment of cells with the four factors Oct, Myc, Klf, and Sox.

However, the applicant has successfully put aside these concerns. Furthermore, moral issues have not been discussed during prosecution, which suggests that, after the Enlarged Board of Appeal decision G2/06 ("WARF", according to which hES cells are banned from patentability as long as their preparation involves the use of a human embryo), the EPO seems to accept that iPS cells do not fall under this exclusion.

Provided the latter is granted with a similar scope, two conflicting patents would exist in Europe, having the following scope: (Table 2).

Groups working under the Sakurada protocol would probably infringe the Yamanaka patent, in case they use a cytokine or Myc in addition to the other factors. In case Myc was left away, and no cytokine was used, the Yamanaka patent would probably not be infringed.

On the other hand, groups working under the Yamanaka protocol would probably infringe the Sakurada patent, if granted as shown above, in the event that they use Sox and HDACi in addition to the other factors.

Companies working with iPS cells should be aware of this confusing situation and ask for expert counsel before they enter the marketplace with their products.

In Feb 2011, iPierian announced that they have entered into a series of IP agreements with Kyoto University, home of iPS pioneer Shinya Yamanaka, under which iPierian assigns its iPS portfolio to Kyoto University, while the latter grants non-exclusive worldwide rights to its iPS portfolio for use in drug discovery and development. As part of the agreement, Professor Shinya Yamanaka has joined iPierian's Scientific Advisory Board.

This deal illustrates the complicated relationship between both patent portfolios. Further, the deal demonstrates that, at least today, the major goal of iPS technologies is drug development (rather than the oft-cited regenerative medicine).

On May 3, 2012, an opposition was filed against Kyoto University's Yamanaka patent EP1970446. The opposition was lodged by UK law firm Olswang LLLP, without disclosing the true claimant. Proceedings are ongoing at the editorial date.

However, the EPO does not seem to consider iPS cells as falling under the exemptions related to human embryos, and their use. The ECJ has not discussed this type of cells in his the Brüstle decision, and it can thus be considered as granted that these cells remain patentable in Europe, being subject to the same bars as inventions from other fields of technology, i.e., novelty, inventive step, and industrial applicability.

6 Adult Stem Cells

Adult stem cells, also called "Pluripotent germline stem cells (pGSs)", are pluripotent cells which will, without further steps, not redifferentiate to totipotent cells.

Examples are spermatogonial Stem cells or pluripotent somatic Stem cells, *e.g.*, from umbilical chord, from skin of people with Friedreich's ataxia, or enterogastric neural stem cells. It is unlikely that ECJ will consider these cells as "embryos", or as a "human body in a stage of formation". The BGH has not addressed this issue, so the ECJ will most probably not opine on these cells.

7 Cells Obtained by Transdifferentiation

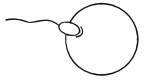
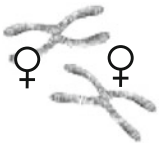
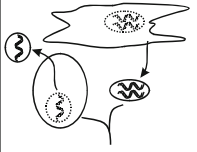
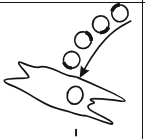
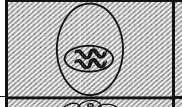
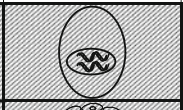
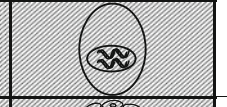
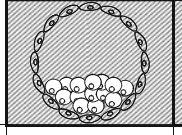
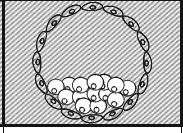
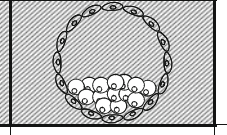
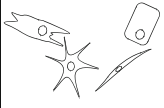
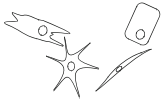
Vierbuchen et al. (Nature 463, 1035-1041) have transdifferentiated fibroblasts to nerve cells with only two transcription factors (BAM and BAZ). This means that no detour via pluripotent cells, stem cells, or blastocysts is necessary. The cells do thus never reach a stage which can be considered "embryonic" according to common understanding.

It is, thus, quite unlikely that ECJ will consider these cells as "embryos", or as a "human body in a stage of formation". However, the BGH has not addressed this issue in his referral and, accordingly, the ECJ has noted considered these cells in his decision.

8 Methods Which Allow the Production of hES Cells Without Destroying an Embryo

What if methods were available which allow the production of hES cells without destroying an embryo? In a letter to former President Bush, Leon Kass, who was the chair of the President's Council on Bioethics, envisaged in May 2005 that such

Table 3 Different methods to derive stem cells, or to transdifferentiate cells. Shaded areas sow what the ECJ considers as an embryo

Type	Potency status	Human embryonic stem cells	Cells obtained by parthenogenesis	Cells obtained with SNCT	Adult stem cells	Induced pluripotent stem cells	Cells obtained by transdifferentiation
							
Oocyte	Totipotent						
Blastomere and/or blastocyst	Totipotent						
Stem cell	Pluripotent						
Progenitor cell	Multi-oder oligopotent						

approach would probably guide a way to a solution out of the ethical dilemma posed by hES cell research.

Later in 2005, S. Matthew Liao discussed for the first time the "Blastocyst Transfer Method". He hypothesized that this method, in which cells from the inner cells mass of a blastocyst (<125 cells) could be extracted and used for the production of hES cells without destroying the latter and, specifically, without harming its chance of developing into a healthy functioning individual.

In 2006, Klimanskaya et al. reported about the successful derivation of hES cells from cells obtained by biopsy of a human blastomere (8–20 cells), which survived this incident. This approach has been termed "Blastomere extraction".

Both authors discussed the possibility that the embryo could still be implanted and brought to term. Notably, a similar approach is already applied in preimplantation genetic diagnosis (PGD), where one or more cells are sampled from a blastocyst obtained by in vitro fertilization and undergo molecular screening, while the remaining blastocyst is then implanted into a mother. Success rates of 44 % have been reported for such approach, e.g., by the Guy's and St Thomas' Centre for Preimplantation Genetic Diagnosis.

Although PGD, and the invasive treatment the embryo is subjected to therewith, finds increasing acceptance among parents, it is hard to imagine that the latter would agree with such treatment only to allow researches to obtain hES cells from their embryo.

This means that, although an embryo would probably survive such treatment, it is unlikely that it would be implanted thereafter. It would rather have to go back into the freezer to preserve, at least theoretically, its potential to develop and differentiate to a fetus, and eventually be born. Even then, however, one would probably assume that the embryo has not been killed or destroyed by the extraction process.

Although different authors object these approaches as like ethically problematic (Holm 2005) and thus unsuitable to render hES cell research ethically acceptable, these approaches could at least bypass the exclusion set forth by the Biopatent directive under Art 6(c), according to which the use of human embryos for industrial or commercial purposes shall be considered unpatentable. While embryos would still be "used" in such process, they would at least not be "destroyed", how the ECJ has put it in the Brüstle decision.

However, the ECJ has also ruled that inventions using human embryos are patentable for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it. However, even if the suggested methods of Blastocyst Transfer and Blastomere Extraction do not destroy the embryo, they are are most probably not useful to the embryo itself.

As the ECJ ruled that the exclusion from patentability also covers the use of human embryos for purposes of scientific research, (because the grant of a patent imply its later industrial or commercial application) it is quite likely that obtaining hES cells with Blastocyst Transfer and Blastomere Extraction would still be considered exempt from patent protection by the ECJ Table 3.

References

Bergman K, Graff GD (2007) Nat Biotechnol 25:419–424
Caulfield T et al (2009) Nature reports stem cells doi:10.1038/stemcells.2009.61
Holm S (2005) Am J Bioeth 5(6):20–21
Hüttermann A, Storz U (2010) Monsanto soy bean patent cases—a paradigm shift gathering in case the ECJ takes over patent jurisdiction, Les Nouvelles, pp 156–159
Kalorma Information (2012) Stem cells: worldwide markets for transplantation and cord blood banking, New York
Klimanskaya I et al (2006) Nature 444:481–485
Liao SM (2005) Rescuing human embryonic stem cell research: the blastocyst transfer method. Am J Bioeth 5(6):8–16
Rabin S (2005) Nat Biotechnol 23(7):817–819
Visiongain Ltd (2012) Stem cell technologies: world market outlook 2012–2022, London

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