PATENTING OF STEM CELLS AND PROCESSES INVOLVING STEM CELLS ACCORDING TO THE RULES OF THE EUROPEAN PATENT CONVENTION (EPC)

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Stem cells are undifferentiated cells that on the one hand divide over a long period of time regardless of their origin and can therefore "self-renew" without concomitant differentiation, but on the other hand can differentiate into specialized cells after appropriate stimulation. On the basis of these properties it is hoped that sooner or later it will be possible to use human stem cells for treatment of diseases caused by a defective or inadequate functioning of certain cells. The best-known examples of such diseases are Parkinson's Disease, juvenile diabetes, and myocardial diseases. The *Handelsblatt* estimated the economic potential of human stem cells at 360 billion US$ in 2001. Since ever more potential fields of use are being added in the course of time, such as screening and testing of active substances, the actual economic potential is probably now far higher.

However, human stem cells have made headlines not only because of the possible therapeutic uses they may open up, but also because of the legal and ethical problems associated with obtaining and using them. The judiciary and legislators have made efforts to keep step with development, but find themselves confronted with enormous difficulties. While on the one hand knowledge of human stem cells is growing rapidly, there is still uncertainty concerning the fundamental differences between the various types of stem cells and their particular potential. Then again, legal regulations stand against the final clarification of the potential, such as is in Germany's case with the Embryo Protection Act.

From the wide problem area of "stem cells," only a small section, namely the patenting of human stem cells at the European Patent Office, will be dealt with in this paper. The common definitions of the various types of stem cells will first be presented, and then the legal basis for patenting and current practice of the European Patent Office are considered.

Definition of stem cell types

In stem cell research, a distinction is made between three basic types of human stem cells, namely a) embryonic stem cells, which are often abbreviated to "ES," b) embryonic germ cells, abbreviated to "EG," and c) adult stem cells. The first two types have the common feature of being initially undifferentiated, dividing for some time ("self-renewing") and finally being able to differentiate into specialized cells. However, they differ in the degree of ability for self-renewal, i.e. the duration of their ability to divide, and in the extent of their ability to differentiate.

Embryonic stem cells are obtained from embryos not more than one week old. An embryo in this stage is called a blastocyst and essentially consists of three structures: an outer envelope cell, the trophoblast, which is responsible for implantation in the uterus at a later stage of development and from which the placenta develops; a hollow space defined by the envelope of the trophoblast, the blastocele; and an inner cell mass, which contains approximately 30 cells in an embryo four to five days old. The cells of this inner cell mass are at least pluripotent: they can develop into skin cells, nerve cells, muscle cells, blood cells, and any of the other known 220 cell types that form the tissue and organs in a human body. Whether these cells are totipotent - that is

to say whether they could give rise to a complete organism - is in dispute and is currently regarded as rather improbable. Unfortunately, the applicability of several rules, which restrict the patentability of inventions, depends on the answer to precisely this question.

When the inner cell mass is taken from a four to five day-old blastocyst and is cultured *in vitro*, it starts to proliferate, i.e. to divide. Embryonic stem cells can probably divide to an unlimited extent: the first human embryonic stem cells ever isolated, obtained in 1998 at the University of Wisconsin-Madison, are still capable of division and are pluripotent. It is this pluripotency that makes the cells of such interest to researchers.

Embryonic germ cells are taken from the early germ line cells of the developing fetus. They are also pluripotent, but do not differentiate with the same reliability as embryonic stem cells into "normal" cells. They are of minor importance to science and research. Totipotency is not discussed for these cells.

Adult stem cells are incompletely differentiated precursor cells that are found in already differentiated (adult) tissue. They are capable of cell division, although not to the same extent as embryonic stem cells, and as a rule can only differentiate into cells of the tissue type from which they are taken. Since development into all 220 cell types is no longer open to them, they are called "multipotent."

Regardless of the origin of an individual stem cell, proliferating stem cells in the undifferentiated state are called "stem cell lines."

<u>Patentability of stem cells and processes concerning stem cells according to the European Patent Convention (EPC)</u>

The scope of protection of a patent is determined by the wording of the granted patent claims. There are two main categories of claims: product claims and process claims, the latter including the similarly frequently chosen category of the use claim. With regard to stem cells and associated processes, the following basic types of claim are possible in principle:

a) Product claims for

- stem cells,
- stem cell lines,
- cell mixtures containing stem cells,
- cells originating from stem cells, e.g. precursor cells,
- genetically modified stem cells, or
- genetically modified stem cell lines.

b) Claims for processes for
- isolation, concentration and/or selection of stem cells,
- culturing of stem cells,
- (genetic) modification of stem cells, and finally
- treatment of patients using stem cells.

Article 52(4) EPC excludes all methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body from patent protection. In European patent applications the treatment claims are therefore replaced by so-called second medical use claims of the following type:

Use of stem cells for the preparation of a medicament for the treatment of disease X

Upon request, a claim of this type will be subjected to examination according to the rules of the European Patent Convention (called "EPC" in the following). According to Article 52(1) EPC, after thorough examination, European patents shall be granted for inventions that are new, based on an inventive step and susceptible to industrial application. Novelty, inventive step, and susceptibility of industrial application are regulated more precisely in Articles 54, 56, and 57 EPC (see Infobox 1) and represent the basic prerequisites for patenting any subject matter or process, regardless of which technical field is involved. These general prerequi-

sites will not be dealt with in the following. Likewise, the requirements an application should meet, e.g. a clear and complete disclosure (Article 83 EPC, see Infobox 1), will not be the subject of the following consideration.

Like any rule and any law, the EPC contains exemptions, and two of these exemptions (see Infobox 2) are of particular importance for the patenting of stem cells or processes that have involved stem cells. The following comments will concentrate on these exemptions.

First exemption: Article 52(2) EPC - Invention versus discovery

Article 52(2) EPC states that, *inter alia*, discoveries are not regarded as inventions. On the basis of this exclusion provision, the patentability of genes and proteins, as well as that of microorganisms and stem cells, has been repeatedly questioned.

To answer the question of whether a stem cell that has been isolated and made reproducibly available is an invention or a discovery, it should be remembered that the patent law term "discovery" differs from the word "discovery" in everyday usage. In everyday usage, it is unimportant whether the discoverer has described a discovery to the public as one that can be reproduced. However, it is precisely here that one finds the small but significant difference between the discovery of everyday use and an invention as understood (or defined) by patent case law: a discovery can become an invention if the discoverer of an object, for example a particular molecule, isolates and characterizes it and makes available a technical teaching that allows the invention to be "reworked," i.e. allows the molecule either to be isolated again according to this teaching or, if the structure has been analyzed, to be synthesized chemically. In other words, a discovery enriches knowledge, while an invention increases ability. The classic example from German court rulings on this question concerns the discovery/ invention of an antibiotic: as long as it is only observed that antibiotically active substances are present in a soil sample, it is a discovery; as soon as the antibiotic has been isolated and characterized and a person skilled in the art could in turn prepare the now characterized antibiotic by either culturing the microorganism that produces the antibiotic or by a synthetic route, it can be seen as an invention. The same would have to apply to stem cells: stem cells *in vivo* are generally not patentable; isolated stem cells or stem cell lines that can be reproduced identically in whatever manner at least do not infringe upon Article 52(2) EPC.

This interpretation is supported by Directive 98/44 EC of the European Parliament and Council of 6th July 1998 on the legal protection of biotechnological inventions ("Biotechnology Directive" in the following). The Biotechnology Directive first confirms generally in Consideration 34 that the terms "invention" and "discovery" as defined by national European or international patent law are not affected by the Directive. With regard to biological material, Article 3(1) (2) of the Biotechnology Directive states:

For the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, prepared, processed or used.

Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature.

More concretely for stem cells, in particular human stem cells, Art. 5(1) (2) of the Biotechnology Directive reads:

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.

An element isolated from the human body or otherwise produced by means of 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.

Accordingly, stem cells and stem cell lines that have been isolated and made reproducibly available, also of human origin, are not regarded as discoveries. Therefore, the exemptions of Article 52(2) EPC should not be an obstacle to the patenting of isolated stem cells or stem cell lines of human origin.

Second exemption: Article 53(a) EPC – Exceptions to patentability

According to Article 53(a) EPC, European patents are not granted with regard to inventions whose publication or exploitation would be contrary to "ordre public" or morality; however, the exploitation shall not be deemed to be contrary merely because the exploitation of the invention is prohibited by law or administrative provisions in some or all of the contracting states.

Accordingly, the limits imposed by the Embryo Protection Act or Stem Cell Act play no role in an evaluation of the question of whether patent protection is possible for a human stem cell or an invention relating to its preparation or use [conversely, granting of a patent also does not mean license to use; this always depends on the admissibility of exploitation of the patent in the particular contracting state, i.e. on the legal regulations of this contracting state].

Article 53(a) EPC is consistent with the identical Article 6(1) of the Biotechnology Directive. In the first clause of both rules, a violation of public order or morality is stated as the criterion. Unfortunately, no concrete definition for these two terms is accepted by all of the EPC contracting states. One of the Boards of Appeal of the European Patent Office that attempted to define "ordre public" and morality in a decision that actually concerned the patentability of plants and plant genes arrived at the following results:

Ordre public

Inventions the exploitation of which is likely to breach public peace or social order (for example, through acts of terrorism) or to seriously prejudice the environment are to be excluded from patentability as being contrary to "ordre public."

Morality

The concept of **morality** is related to the belief that some behavior is right and acceptable whereas other behavior is wrong, this belief being founded on the totality of the accepted norms which are deeply rooted in a particular culture. For the purposes of the EPC, the culture in question is the culture inherent in European society and civilization. Accordingly, under Article 53(a) EPC, inventions the exploitation of which is **not** in conformity with the conventionally-accepted standards of conduct pertaining to this culture are to be excluded from patentability as being contrary to morality.

Even if these definitions were generally acknowledged, they leave much room for discussion. For example, reference is made in this connection to the "European culture" mentioned in the definition of morality. Considering the example that euthanasia legislation and embryo protection are handled differently in the various contracting states of the EPC, it can easily be concluded that diverging concepts of the term "morality" also exist within European culture. Moreover, since the recent accession of Turkey to the

European Patent Convention, consideration of the recognized standards of European culture is probably no longer sufficient. Therefore, it will be almost impossible for any international authority and also for the EPO to develop generally accepted, concrete definitions.

Consistent with Consideration 38, on publishing the Biotechnology Directive, the European Parliament and the Council non-exhaustively listed some inventions for which patents should not be granted even if they should meet all the other criteria of an invention (Article 6(2) of the Biotechnology Directive). The European Patent Office has implemented these exceptions word for word in the rules of the European Patent Convention. In view of the importance of the rules for the subject matter in question, the full wording of the corresponding Rule 23d of the European Patent Convention is reproduced below:

Rule 23d

Exceptions to patentability

Under Article 53 (a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:

(a) processes for cloning human beings;

(b) processes for modifying the germ line genetic identity of human beings;

(c) uses of human embryos for industrial or commercial purposes;

(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

One disadvantage of Rule 23d EPC is the absence of any definitions. A definition of the term “embryo” is critical above all in this connection. Since in some legal systems, e.g. in Germany, any totipotent cell taken from an embryo which, if the necessary further prerequisites exist, is capable of dividing and developing into an individual is already regarded as an embryo (§ 8(1) Embryo Protection Act), the exception of letter (a) could already apply to processes for proliferation of embryonic stem cells, provided of course that these are in fact totipotent, i.e. capable of being developed into a complete living being. A further ambiguity concerns the term “cloning”: it is questionable whether this means a process for the development of a complete organism whose genomic make-up is identical to that of another organism, or whether it includes the simple cell division of an embryonic stem cell, provided this is totipotent and therefore to be regarded as a living being, with the aim of propagation of undifferentiated cells. Rule 23d (a) EPC can therefore be interpreted to mean that processes for propagation of undifferentiated human embryonic stem cells are already regarded as falling under the ban on patenting, or that only processes aimed at producing complete organisms having a genetic make-up that corresponds to that of another organism are unpatentable. The considerations of the Biotechnology Directive are of only limited assistance in this connection. According to Consideration 41, all processes with the aim of creating a human being whose cell nuclei contain the same hereditary information as another living or dead human being are to be regarded as processes for cloning human beings. This does not rule out the application of Rule 23d, letter (a) to totipotent stem cells.

Rule 23d, letter (b) excludes processes for modifying the germ line genetic identity of human beings from patentability. This rule applies to EG cells and human embryonic stem cells, provided that these are totipotent.

Rule 23d, letter (c) prohibits the patenting of processes in which human embryos are used for industrial or commercial purposes. In this respect, Consideration 42 of

the Biotechnology Directive states that inventions which pursue therapeutic or diagnostic purposes and are used on the human embryo for the benefit thereof should not be excluded from patentability.

Rule 23d, letter (d) excludes from patent protection processes for modifying the genetic identity of animals that are likely to cause them suffering without any substantial medical benefit to man or animal; it also excludes patent protection for animals resulting from such processes. This rule is based on a decision of a Technical Board of Appeal of the European Patent Office, in which the patentability of groups of animals was confirmed in principle. In the grounds for this decision, the Board of Appeal found that modifications to genetic identity that lead to the suffering of animals can be regarded as consistent with Article 53(a) EPC only if a benefit of the invention to man or animal outweighs the suffering with which it is associated.

In summary, it can be said that the EPC, interpreted literally, would preclude only the patentability of human embryonic stem cells and germ cells, and then only if these human stem cells were in fact totipotent. In this case, the stem cell could be regarded as a human body and therefore, in accordance with Article 5(1) of the Biotechnology Directive, corresponding to Rule 23e(1) EPC, could represent a non-patentable invention. On the other hand, all human embryonic stem cells that are not totipotent, i.e. all human embryonic stem cells that lack the potential to develop into a complete organism, should be patentable if they meet the other prerequisites for patenting. This applies to pluripotent embryonic stem cells and to multipotent adult stem cells, and furthermore also to mixtures containing these and precursor cells originating from these. Since the law does not differentiate between stem cells and stem cell lines, this conclusion applies accordingly to stem cell lines. Moreover, it is unimportant whether the stem cell is modified or unmodified: Rule 23d (b) EPC prohibits only the patenting of processes for modifying the germ line genetic identity of human beings. The germ line genetic identity of a human being can be modified starting from a stem cell only if a living being can be formed from it, that is to say it is totipotent. Rule 23d (b) EPC does not apply to genetically modified pluripotent and multipotent cells and the processes for their preparation.

In a literal sense, processes for the culturing and proliferation of human embryonic stem cells, i.e. their propagation in the undifferentiated state, can also only be non-patentable if these stem cells are totipotent. In the case of totipotent stem cells, genetic modification of these cells would be prohibited. The patentability of processes for obtaining (isolating, enriching and selecting) human embryonic stem cells depends in turn on the definition of an embryo. For example, blastocysts that are four to five days old are called embryos in Germany, whereas they are regarded as pre-embryos in England. Processes for modifying the germ line genetic identity of humans are generally prohibited; processes for modifying the genetic identity of animals are subject to a proportionality order.

Opinion of the European Group on Ethics in Science and New Technologies of the Commission

In Article 7 of the Biotechnology Directive, the European Parliament and the Council laid down that the European Group on Ethics in Science and New Technologies of the Commission (EGE) should evaluate all the ethical aspects in connection with biotechnology. The EGE, which had stated its opinion on ethical aspects of research and use of human stem cells beforehand (EGE Opinion No. 15), gave its opinion on the ethical aspects of patenting of inventions involving human stem cells in May 2002 (EGE Opinion No. 16). Without wanting to delve into the considerations of the EGE, which are sometimes difficult to reconstruct, the results of their deliberations should be mentioned. In the

opinion of the EGE, isolated, non-modified stem cells do not meet the legal requirement of being susceptible of industrial application and therefore are not patentable. Furthermore, such isolated cells would be so close to the human body, the fetus, or the embryo from which they were isolated that their patenting could be regarded as a type of commercialization of the human body. Unmodified stem cell lines are considered just as unpatentable because they could have a broad range of uses that have not been described hitherto and therefore would lead to patents too wide in scope.

In contrast, stem cell lines modified by *in vitro* treatments or genetic modification and with newly acquired features for a particular industrial use are regarded as patentable. Finally, the patentability of processes that involve human stem cells is regarded as ethically acceptable, regardless of their origin.

It can be seen even from this brief summary that the assessment of the EGE is based at least in part not on ethical considerations, but on patent law criteria. It remains to be seen whether and to what extent Patent Offices, in particular the European Patent Office, will use Opinion No. 16 of the EGE as a well-founded aid to making a decision when evaluating patentability according to Article 53(a).

The current practice of the European Patent Office

The first patent applications relating to embryonic stem cells were filed in 1987. Numbers of applications have steadily increased since 1993, with a peak in 1999. For a long time the applications chiefly originated in the United States, but there are now applications, although in far fewer numbers, from European and, to an even lesser extent, Asian applicants.

European Patent EP695351 B1

It was a European patent that attracted the attention of the public in recent years. The European Patent Office granted the University of Edinburgh the patent with the number EP695351 B1, which related, *inter alia*, to a method of isolating and/or enriching and/or selectively propagating desired animal stem cells (claim 1); animal cells with particular properties, which could also have been stem cells (claim 37); a method of preparing a transgenic animal from a stem cell prepared according to the patent (claim 47); and a method of preparing a transgenic animal, where this method is said to have led to a chimerical animal (claim 48). Claims 1, 37, 47 and 48 are reproduced in the original English wording in Infobox 3. Since in English the term “animal” includes the species man and the description of the patent expressly stated that the term “animal cells” was also to include “human cells,” claims 47 and 48 would have included a method of producing a transgenic (claim 47) or chimerical (claim 48) human. The patent was granted shortly after the European Patent Organization implemented the principles of the Biotechnology Directive in the European Patent Convention. The patent holder, alarmed by four promptly filed oppositions and the reaction of the public, filed new claims within the opposition period, by which, through insertion of the word “non human” before “animal” into claims 47 and 48, the preparation of transgenic humans should have been excluded from patent protection. Fourteen oppositions in total were lodged against the patent.

Oral proceedings took place in July 2002. As a result, the patent was maintained in limited scope. The written grounds of the Opposition Division became accessible in July of this year. These show that the Opposition Division asked whether Rule 23d (c) EPC, by which the use of embryos for industrial or commercial purposes is excluded from patent protection, in fact excludes from patent protection only embryos or also embryonic stem cells obtained from the embryo. After taking various considerations and articles of the Biotechnology Directive into account, the Opposition Division concluded that Rule

23d (c) is to be interpreted broadly, i.e. not only the use of embryos expressly referred to in law, but also the stem cells resulting from the use of embryos are regarded as non-patentable. Urged on by the European Patent Convention, the Opposition Division then gave intensive consideration to the opinion of the EGE, according to which modified embryonic stem cells, such as are claimed in the Edinburgh patent, should have been regarded as patentable. The Opposition Division, however, evaluated the conclusions of the EGE as inconsistent, out of line with general patent law principles, and finally illogical, and declined to take it into consideration when finding its judgment. The main request of the patent holder, which differed from the granted patent only with regard to claims 47 and 48 with the insertion of the term "non-human" as already mentioned, was not allowed. Maintenance of the patent in the amended scope was only agreed to after human embryonic stem cells were explicitly excluded both in the process claims and in the product claims. Claims 47 and 48 were omitted in total.

European Patent Application EP770125

With European Patent Application EP770125, the “father” of cell cultures of human embryonic stem cells is attempting to patent these cell cultures and a process for obtaining such cell cultures. In this case, the European Patent Office has pointed out in a first examination report that it emerges from the description that the human embryonic stem cells would have been obtained by “irreversible destruction” of human embryos. Such a use of human embryos is not patentable under Rule 23d (c) EPC; the same applies to products resulting from these. It should be noted that the applicant did not claim the use of embryos themselves, but exclusively claimed the resulting culture of embryonic stem cells. The Examining Division referred to the fact that Consideration 42 of the Biotechnology Directive allowed an exception only if the use of an embryo was an invention that included a therapeutic or diagnostic purpose to the advantage of the embryo, which obviously was not the case here.

In this case, an instance of the European Patent Office goes far beyond the wording of the law in that it does not allow the product claim, permitted by law, for a human embryonic stem cell (see Rule 23e (2) EPC) and as a reason states that the preparation of the product does not have access to patent protection. In his response to the decision, the applicant’s agent pointed out that the claims are directed towards cell cultures and processes for the use of these cell cultures, and not to the use of a human embryo. Furthermore, the cells of a human embryonic stem cell line are induced for the purpose of proliferation, whereby they differ from the human embryonic stem cells, which exist *in vivo.* It remains to be seen how the European Patent Offices receives this reasoning.

European Patent Application EP1040185

This patent application relates to isolated purified precursor cells from stem cells, which are non-tumorigenic after transplantation into the nervous system and have neuronal or glial properties, and processes for their preparation, which start from embryonic stem cells that can be isolated from a number of different mammals, *inter alia* also from human embryos. Here again, Article 53(a) EPC and Rule 23d EPC play a prominent role in the examination proceeding, although alongside further objections with regard to novelty, inventive step and reworkability. With regard to the cell compositions claimed, the European Patent Office in turn argues that the destruction of human embryos is absolutely necessary for their preparation, and therefore according to Rule 23d (c) EPC and Article 53(a) EPC these compositions are not patentable. The Examining Division here also rejects the argument that already established cell lines are used, since these are not infinitely usable and sooner or later there will be a need for new embryonic stem cells. Furthermore, in the communities of

the EPC member states there would be significant numbers who would see morality disregarded by the destruction of embryos to provide embryonic stem cells.

Another objection worth mentioning concerns the genetically modified neuronal precursor cells, which, according to the description, are modified in the stage of the embryonic stem cells. The Examining Division argued that embryonic stem cells belong to the germ line, since they have the potential to form germ cells, and therefore lead to a modification of the germ line genetic identity of man. Processes in this respect are again to be excluded from patenting, in accordance with Rule 23d (b) EPC.

Summary of the current practice of the European Patent Office

All three proceedings discussed above have the common feature that the first instance Divisions of the European Patent Office (Opposition Division in the case of the Edinburgh patent, Examining Divisions in the other two cases) interpret the EPC far beyond its wording, in that from the ban on the use of human embryos for industrial or commercial purposes laid down in Rule 23d (c) EPC they also extrapolate a ban on stem cells of whatever potency, if their preparation at one time involved the use of embryos. The justification given for this in all three cases discussed assumes that if Rule 23d (c) EPC in fact relates only to the use of human embryos, then a redundancy exists with Rule 23e (1) EPC (see Infobox 4). The legislators cannot have intended such an alleged redundancy, so Rule 23d (c) EPC must imply more than only the ban on use. This justification seems questionable, at least.

The decision of the Opposition Division on EP695351 briefly summarized and explained above is not yet final. The parties involved could have lodged an appeal against the decision by September 30, 2003. At the time of compiling this paper it appears from the official register of the EPO that the proprietor made use of this legal possibility. Therefore, it is hoped that a Board of Appeal will comment on the matter of the patentability of human embryonic stem cells and the processes for their preparation, maintenance, and use in the not too distant future.

In one of the two cases discussed above that are still in examination proceedings, processes for the genetic modification of human embryonic stem cells have been described as non-patentable since embryonic stem cells can develop into germ cells on the basis of their pluripotency. The modification of the germ line genetic identity again is excluded from patentability by Rule 23e (b) EPC.

This conclusion cannot be denied a certain inner logic in the case of totipotent stem or germ cells, since these could develop into a human being with a modified germ line. However, if the objections of the Examining Division relate merely to the fact of the possible formation of modified germ cells from the pluripotent stem cells, it should be noted that the modification of germ cells as such is not excluded from patent protection. The restrictions of the legislators appropriately relate to the germ line and not to germ cells.

Finally, it remains to be said that many of the problems associated with the patenting of human embryonic stem cells can certainly only come close to being resolved when the question of the potency of embryonic stem and germ cells is finally clarified. Until this matter is settled, the sword of Damocles of Rule 23e (1) EPC hangs over every patent application: “The human body in the individual phases of its formation and development and (...) cannot represent patentable inventions.” Whether these circumstances will have an influence on the therapeutic potential of embryonic stem cells or their use by industry remains to be seen.

Infobox 1

Article 54 - Novelty

(1) An invention shall be considered to be new if it does not form part of the state of the art.

(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

(3) Additionally, the content of European patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Article 93 on or after that date, shall be considered as comprised in the state of the art.

(4) Paragraph 3 shall be applied only in so far as a Contracting State designated in respect of the later application, was also designated in respect of the earlier application as published.

(5) The provisions of paragraphs 1 to 4 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.

Article 56 - Inventive Step

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. If the state of the art also includes documents within the meaning of Article 54, paragraph 3, these documents are not to be

Article 57 - Industrial Application

An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.

Article 83 - Disclosure of the invention

The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Infobox 2

Article 52 - Patentable Inventions

(1) European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step.

(2) The following in particular shall not be regarded as inventions within the meaning of paragraph 1:

(a) discoveries, scientific theories and mathematical methods;

(b) …

Article 53 - Exceptions to Patentability

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 to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;

(b) …

Infobox 3

Claims 1, 37, 47, and 48 of EP 695 351 B1

1. A method of isolating and/or enriching and/or selectively propagating desired animal stem cells, which comprises maintaining a source of said cells under culture conditions conducive to cell survival, characterised in that the source of cells includes stem cells containing a selectable marker which is capable of differential expression in (a) desired stem cells of said source and (b) cells of said source other than the desired stem cells, whereby differential expression of said selectable marker results in preferential isolation and/or survival and/or division of the desired stem cells containing the said selectable marker.

37. An animal cell capable of being cultured to form a mixture of cells including desired stem cells and cells other than the desired stem cells, characterised in that all cells in the said mixture of cells contain a selectable marker and that in the said mixture of cells, under appropriate selective culture conditions, differential expression of the selectable marker in (a) the desired stem cells and (b) cells other than the desired stem cells enables selective survival or growth of the desired stem cells to occur, so as to enable isolation and/or enrichment and/or propagation of desired stem cells.

47. A method of preparing a transgenic animal comprising obtaining a desired stem cell according to the method of any of claims 1-36, excising the selectable marker from the desired stem cell and generating the transgenic animal therefrom.

48. A method of preparing a transgenic animal, said animal comprising a selectable marker capable of differential expression in (a) desired stem cells and (b) cells other than desired stem cells, the method 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 chimaeric animal to enable germline transmission of the selectable marker.

Infobox 4

Rule 23e (1)
The human body and its elements

(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.

(2) …