Dissenting Opinion on Stem Cell Report

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This document is a dissenting opinion to the Report on patents in the field of human stem cells (hereinafter referred to as the "*Report*") of the Expert Group on the development and implications of patent law in the field of biotechnology and genetic engineering (E02973). As in the *Report*, this dissenting opinion is focused on human stem cells, human embryos and gametes as well as the application of the *ordre public* and morality clause of Art. 53 EPC and the respective Articles 5 and 6 in the Directive 98/44/EC.

Summary

- The *Report* does not object to "non-destructive uses" of human embryos (cf. *Report*, page 18). Article 6(2)c of the Directive, however, considers unpatentable "uses of human embryos for industrial or commercial purposes" and does not distinguish between "destructive" and "non-destructive" uses of human embryos. It is arbitrary to exclude "destructive uses" from patentability and to allow "non-destructive" uses of human embryos.
- Even if "non-destructive" uses of human embryos were deemed patentable, the method disclosed in Chung et al. 2008 does not provide sound evidence for a "non-destructive" use of human embryos, contrary to the *Report* (page 20)
- Stem cells derived from activated human egg cells (parthenogenetic embryonic stem cells, hpES) are not identical to human embryonic stem cells, and therefore it is inadmissible to grant patents for processes and products on human embryonic stem cells, based on such hpES methods.
- Novel methods enable the use of iPS or embryonic stem cells to create artificial gametes and embryos genetically derived from two partners of same sex or from one individual only. It is recommended that both the European Commission and the EPO specify and clarify that the term "germ cell" also includes artificially created egg and sperm cells, and that the term embryo also covers those artificially fused embryos.
- Genome editing technologies such as CRISPR have reignited the debate on human germline modification. It is paramount that both the European Commission and the EPO specify and clarify that Articles 6(2)b and 6(2)c apply to CRISPR-Cas9 and CRISPR-Cpf1, if practiced in human germ cells and human embryos.
- Transparency and accountability of the work of the EPO requires disclosure of data on patent applications and grants, and revelation of changed granting practices in the EPO's Guidelines for Examination.

There is a strong need for a better balance in patent law to secure the proper interpretation of the *ordre public* and morality exemption in European patent law, in accordance with the purposes and intentions of the European legislator and with the EU's Charter of Fundamental Rights. This requires the European Commission to take the initiative in strengthening the patent exclusions in Articles 5 and 6. In view of the rapid scientific developments it is urgently needed to provide an adequate clarification and precise guidance for the correct interpretation of the Directive 98/44/EC. This would comprise the following possibilities:

- new binding rules for the interpretation of current patent law without changing the text of the Directive 98/44/EC;
- a separate legislative action without altering the Directive as such;
- a legislative action in order to incorporate robust and legally defined limits into the Directive 98/44/EC .

Taking no political action is not and cannot be an option.

1. Introduction

Two members of the Expert Group could not consent to the Stem Cell *Report* and its opinion, even though these members share the majority's view that several ambiguities of the Biotech Directive with respect to human embryos have been sufficiently clarified by two CJEU decisions. However, in the members' opinion, the *Report* does not provide the basis for a balanced judgment, as several facts and perspectives have been downplayed or ignored. Lamentably, a number of important recent scientific developments in biotechnology, such as CRISPR genome editing as well as the creation of artificial gametes and embryos from stem cells, which have implications for patent law were also not taken up adequately, despite many attempts to address them within the Expert Group. The report is therefore unbalanced, as it did not appropriately represent diverging views on stem cell patentability and excluded further scientific developments which are relevant to the mission of the expert group and the provisions set in Article 16 of the Directive 98/44/EC:

2. A teleological and historical interpretation of Directive 98/44/EC is needed

The Report correctly enumerates relevant legislative articles and case law. In its interpretation, however, the Report is to a large extent confined to the literal meaning of the statutory text. In contrast, this dissenting opinion considers it necessary to recall the legislative history to reveal the intent of the legislator and also to apply a teleological interpretation which takes the purpose of the law into account.

Therefore, this dissenting opinion departs from the view that in codifying Articles 5 and 6 of the Biotech Patent Directive, the European legislator has created a genuine European *ordre public* which must be respected and should not be undermined by skilful drafting of patent claims or by twisting the law.[1] Inclusion of these Articles 5 and 6 were central preconditions for the European Parliament to pass Directive 98/44/EC in 1998, which it had rejected in 1995. These Articles and the respective Recitals preserve the democratic process of interpreting the *ordre public* clause in European patent law as a public policy clause. [2] Such

1 See CJEU Brüstle v Greenpeace; EPO Enlarged Board of Appeal Decision G2/06 (WARF); and Comments of the President of the EPO on G2/06, 2006:

2 The author's opinion is based on the insights into European Patent Governance gained in her academic work in which she has traced in detail more than two decades of the controversial legislative history of Directive 98/44/EC, from its first Agenda Setting in 1988 to its final adoption in 1998, and subsequent contentions on the implementation in all the members states in the EU and in the EPC. To this purpose, she has conducted thorough analyses of legal and policy documents and interviews with dozens of MEPs, legal scholars, and stakeholders. The analysis was successfully accepted as her habilitation thesis in political science in 2009 and was published as "The European Patent System. Shifts in Governance through Parliaments and Civil Society" in 2010 ("Das Europäische Patentsystem. Wandel von Governance durch Parlamente und Zivilgesellschaft", 771 pp., Frankfurt/New York: Campus). Parts of the analysis are available in English, e.g.: Schneider, I.: Can patent legislation make a difference? Bringing parliaments and civil society into patent governance, in: Haunss/ Shadlen (eds) The Politics of Intellectual Property: Contestation over the Ownership, Use, and Control of Knowledge and Information. Edward Elgar, 2009, pp. 129-157, and in: Schneider, I.: To Be or not IP? Exploring

an understanding, as expressed in the Biotech Patent Directive, has incorporated two meanings and rationalities: First, the *ordre public* and public policy objections to patentability testify for a constitutionalisation of patent law, in which such clauses introduce constitutional standards for integrating patent law into the general European order of fundamental norms and values.[3] Second, the legal concept of "*ordre public* and morality" was interpreted by the European legislator with respect to consequentialist considerations: Patent law should be harnessed as one of several means to provide for innovation policies which are responsible, sustainable, and promote public welfare. The latter entails a modern understanding of patent governance as a mode of pro-active, socio-political regulation of technological trajectories, in accordance with European social values and norms as enshrined in the Charter of Fundamental Rights and in the precautionary principle.

Such a shift in the understanding of patent governance has resulted in special specifications and a non-exhaustive list of exclusions. For example. in exempting "(a) processes for cloning human beings; and (b) processes for modifying the germ line genetic identity" in Articles 6(2), the EU legislator has regulated scientific inventions which at that time were not yet feasible. The EU legislator thus provided patent legislation based on an anticipatory impact assessment, in which certain techniques were excluded from patentability because they were considered socially undesirable. Pursuing the idea of an ex-ante control of the social desirability of an invention, non-patent eligibility serves to express the societal disapproval of an invention. It is assumed that non-patentability induces a disincentive for respective research and development. It must be emphasised, however, that non-patentability is not penal prohibition. It only removes an incentive - the legal exclusivity of said invention and the expected return on investment - and thus it is used as an indirect mode of regulating R&D without forestalling the freedom of research.

Taken this understanding of Directive 98/44/EC into account, it would be inadequate to restrict the substance of these provisions by a too narrow or merely formalistic interpretation.[4] Implementing the law in both letter and spirit must become an integral part of granting practices at the European Patent Office, the national patent offices, of Case Law, and of interpretations issued by the European Commission.

3. More empirical facts, statistics, and contexts must be taken into account

Another prerequisite for a report "on the development and implications of patent law in the field of biotechnology and genetic engineering" (Art. 16 (c), Directive 98/44/EC) would be to provide an account of the scientific evidence and empirical developments in science, law, economy and society in the field of stem cells.

Even though the *Report* gives in its Chapter 1 a short "overview of the relevant technology", it pays inadequate attention to the big shifts in the field of stem cell research which were caused by the advent of induced pluripotent stem cells (iPS cells) as another type of

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limits within patent law for the constitutionalization of intellectual property rights and the governance of synthetic biology in human health, in: Law and the Human Genome Review, No. 37, 2012, pp. 193-233.

[3] Geiger, Christophe 2006: "Constitutionalising" Intellectual Property Law? The Influence of Fundamental Rights on Intellectual Property in the European Union, in: International Review of Intellectual Property and Competition Law 37: 371-406; Kersten, Jens 2004: Das Klonen von Menschen. Eine verfassungs-, europa- und völkerrechtliche Kritik. Tübingen: Mohr Siebeck Torremans, Paul L.C. (ed.) 2015: Intellectual Property Law and Human Rights. Alphen: Kluwer Law International, 3rd revised edition

[4] "It must be borne in mind, further, that the meaning and scope of terms for which European Union law provides no definition must be determined by considering, inter alia, the context in which they occur and the purposes of the rules of which they form part." (CJEU, C-34/10, par. 31).

pluripotent stem cells that can be generated directly by reprogramming from mature adult cells. The iPS technology was pioneered in 2006 by Shinya Yamanaka in Japan and awarded the Nobel Prize in 2012. iPS has offered the means of producing patient-tailored cells without recourse to embryo destruction or cloning (SCNT). In contrast to human embryonic stem cells, iPS must not be derived from human embryos and can be used to create individual, patient-matched stem cell lines which in the future could be used to generate transplants without the risk of immune rejection. The field of adult stem cells has also developed further, and trans-differentiation of adult cells into other cells also allows for the preparation of patient-specific cells.[5] Thus, many technologies are available today which not only allow bypassing the need for human embryos, but also provide unlimited supplies of autologous cells. Therefore, the ethical controversies around human embryonic stem cells can largely be avoided by these new means. The advent of iPS cells has definitely changed the scientific field and mitigated the ethical debate because other sources of stem cells which do not rely on the use of human embryos have become available. Unfortunately, the *Report* concentrates on five "alternative" methods for deriving human ES cells which are hardly, if at all, used in experimental practices and - especially in comparison to iPS cells - are not in common use. This focus apparently has strategic and legal rather than scientific reasons.

The *Report* also fails to state that, by and large, the field of pluripotent stem cells is still in the stage of basic research, with very few clinical trials carried out to date. Moreover, as an expert hearing has confirmed, many hurdles and risks have to be overcome until therapeutic applications, both for iPS and embryonic stem cells, can become a clinical reality. Therefore, honest scientists have repeatedly warned against promising too much too early. Based on their characteristics of unlimited self-renewal and high proliferation rate, the risks associated with all pluripotent stem cell therapies include tumour formation, unwanted immune responses, and the transmission of infectious or other agents. [6]

To date, several of the first broad patents on embryonic stem cells are soon to expire because they were filed 20 years ago. The European Patent Office has declined to provide statistics for the *Report* on the number of pending patent applications which involve human embryonic stem cells. Numbers, however, are important.

According to patent information based on the Global Patent Index, from 1986 to 2014 1476 patent applications involving human embryonic stem cells were filed as PCT applications, and 1019 European patent applications were filed at the EPO. According to the same source, by 2014 157 respective embryonic stem cell patents had been granted (See *Table 1* in Annex). *Table 2* (in Annex) lists respective embryonic stem cell patent applications per year from 1986 to 2014. It shows that up until 2008 fewer than 100 embryonic stem cell applications were published per year, with a steady increase up to the peak of 131 European patent applications in 2012 at the EPO. According to another statistics provided by the EPO

[5] See for instance: Dave S 2014: Mesenchymal stem cells derived in vitro transdifferentiated insulin-producing cells: A new approach to treat type 1 diabetes. Adv Biomed Res. 2014 Dec 31;3:266; Forcales SV 2015: Potential of adipose-derived stem cells in muscular regenerative therapies. Front Aging Neurosci. 2015 Jul 13;7:123. doi: 10.3389/fnagi.2015.00123. eCollection 2015; Novak D, Weina K, Utikal J From skin to other cell types of the body. J Dtsch Dermatol Ges. 2014 Sep;12(9):789-92.

[6] This was the conclusion in the expert group's hearing with Prof. Peter Andrews on 16 September 2014, and it is also state of the art in scientific reviews. See Herberts, Carla A, Kwa, Marcel SG, Hermsen, Harm 2011: Risk factors in the development of stem cell therapy, J. of Translational Medicine 9, 29, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070641/pdf/1479-5876-9-29.pdf.

in the course of the expert group's debates, and based on manual sorting of cases, applications reached a peak in 2011/2012 at about 105 PCT embryonic stem cell patent applications per year, and 100 respective European applications, and ranged between 20 and 100 EP embryonic stem cell patent applications per year between 2001 and 2013 (See *Table 3* in Annex).

Another counting method, based on manual examination of European patents granted on methods and products which include claims on human embryonic stem cells, has revealed 68 patents granted by the EPO from 1996 to 2015 (Information provided by Dr Ruth Tippe, 24.11.2015).

As the EPO's patent granting practice had been protracted due to legal uncertainties, a large number of patent applications involving human embryonic stem cells are still due to be granted. Therefore, the actual granting practice of the EPO matters.

Controversies concerning the EPO granting patents in the field of human embryonic stem cells started in 2000 at the occasion of the Edinburgh patent (EP 0695351), which sparked high media attention worldwide and for which the EPO admitted that it had granted the patent erroneously.[7] In the opposition proceeding, not only Greenpeace but also several EU member states, namely Germany, Italy, and the Netherlands, were among the 14 opponents. Another important case law at the EPO was the WARF Case and its subsequent ruling G2/06 by the EPO's Enlarged Board of Appeal.

The first CJEU decision in Case C-34/10 Brüstle v. Greenpeace was fully in line with the former decisions of the EPO's judiciary and provided broad definitions for the term "human embryo", which hitherto had not been legally defined in EU law, and of the term "use for commercial and industrial purposes". The second CJEU decision in Case C-364/13 clarified "that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo' (...) if, in the light of current scientific knowledge, it does not, in itself, have the inherent capacity of developing into a human being". Even though judgements by the CJEU on the interpretation of Directive 98/44/EG are not binding for the EPO, they are considered to be persuasive (T 2221/10 und T 441/13).

Despite these clear rules set in both the European Patent Organisation's and EU's jurisdictions, the EPO's granting practice has managed to grant patents around the prohibitions under Art. 53(a) and in Rule 28(c) (formerly Rule 23d c) EPC):

In 2013, the EPO took a single scientific publication by Chang et al. 2008 as justification to allow patents on products and processes "indirectly" derived from hESC, taking 10 January 2008 as a cut-off date. This practice was not revealed in the Guidelines for Examination, but was circulated in presentations of EPO examiners at patent law conferences and was later included in T1441/13**.**

In October 2015, the EPO in its granting practice preponed this cut-off date towards 5 June 2003 based on a protocol to derive human parthenogenetic embryonic stem (hpES) cells from activated oocytes (parthenotes) which was disclosed in the PCT application WO 03/046141. This international patent application was filed as European patent EP1456374. It contained only one claim, was only briefly examined, and was silently withdrawn on 25 November 2009 after fees were not paid several times.

[7] See Schneider 2010 (Footnote 2), p. 403ff.

Respectively, the EPO revised its Guidelines for Examination again (valid from 1 November 2015, Part G Chapter 5.3. (iii), see Annex 4 in the *Report*). Hence, the current EPO practice does allow for granting patents with claims involving human embryonic stem cells if such patent applications are filed after 5 June 2003 and other EPC conditions are met.

This dissenting opinion argues, contrary to the *Report*, that the current EPO practice does not comply with the provisions set in Directive 98/44/EC. To this purpose, it articulates a different interpretation of several legal provisions in the light of scientific developments, together with recommendations for clarification and specification by the European Commission.

4. Article 6(2)c prohibits patentability of *all* third uses of human embryos

Article 6 (2) c of the Directive considered unpatentable "uses of human embryos for industrial or commercial purposes". The Directive does not distinguish between "destructive" and "non-destructive" uses of human embryos. Therefore, the Directive can only mean both possibilities of embryo use. If the legislator had intended to restrict the use to "non-destructive uses", it would have provided respective clarification in the Article and/or in the Recitals. It is arbitrary to exclude "destructive uses" and to allow "non-destructive" uses of human embryos.

Furthermore, the term "use" in patent law is normally understood in broad terms, for instance in the rules on second or further medical use of known pharmaceutical products.[8]

Moreover, the CJEU in Case C-34/10 also states that Article 6 (2) c "includes any invention of patentability wherein the technical teaching which is the subject matter of the patent application requires the prior destruction of human embryos or their use as a base material, whatever the stage at which that takes place and even if the description of the technical teaching claimed does not refer to the use of human embryos" (*Emphasis added*). The CJEU has not suggested that it wanted to allow non-destructive uses of human embryos, and there is no CJEU decision which has explicitly allowed it.

Therefore, the term "*or* their use as base material" must be interpreted as excluding *any* use of a human embryo from patentability, unless the invention is "for therapeutic and diagnostic purposes which are applied to the human embryo and are useful to it" (Recital 42).

In conclusion, only a broad interpretation of the term "uses" of human embryos in Article 6(2)b is in compliance with the Directive.

This interpretation has already been backed by the ruling of the EPO's opposition division in the "Edinburgh" case. Here, the board stated that "only a broad ruling of Rule 23d(c) can have been intended" by the European legislator:[9]

> "If the legislator had intended a narrow interpretation of Rule 23d(c) (...) he would not have introduced both Rule 23d(c) and Rule 23e(1) into the EPC or correspondingly, Article 5(1) and Article 6(2)(c) in the Directive. Rule 23e(1) EPC excludes from patentability the human body, at the various stages of its formation and development, and recital 16 even states that the human body at any stage in its formation and development cannot be patented. The human embryo being an early stage in the development of the human body is thus already included in the scope of Rule 23e(1) EPC, and therefore, a narrow interpretation of Rule 23d(c) EPC would

[8] Second medical indication, EPO Guidelines for Examination; G. VI, 7.1.

[9] The former Rule 23d (c) EPC is now Rule 28(c), the former Rule 23e(1) is now Rule 29(1) EPC.

> result in a 'redundancy' over Rule 23e(1) EPC. The fact that Rule 23d(c) EPC refers to 'uses' for 'industrial or commercial purposes' is not of relevance in the given context. (...) If the patenting of a product is ethically unacceptable, it is hardly conceivable that the patenting of 'uses' of this product can be judged differently. Thus it is considered that the exclusion of human embryos from patentability under Rule 23e(1) also pertains to the 'uses' of human embryos for whatever purpose."[10]

As already stated as a minority opinion in the *Report*, the broad exclusion of *any* use of human embryos for third party interests is also backed by the legislative history of Article 6(2)c of the Directive 98/44.[11] And even if the CJEU in Case C-34/10 Brüstle v Greenpeace had been completely silent about "prior destruction of human embryos", it would be a logical fallacy to deduce that this would then allow patentability of "non-destructive" uses of human embryos. The court was just not asked to judge this question.

In addition, it must be emphasised that the list of inventions in Art 6(2) of the Directive 98/44 is non-exhaustive and therefore does not enumerate all possible uses intended by the legislator. Several Recitals (38 to 40) already provide further examples, for instance Recital 38 which states that "processes, the use of which offend against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals, are obviously also excluded from patentability".

The patent exclusion in Article 6 (2) c of the Directive 98/44 is based on the Kantian rationale for human dignity, which states that humans must always be treated as an end in itself and not as a mere means to an end. Reference to human dignity as a fundamental norm for the interpretation of the Directive is also made in Recital 16, reassured in CJEU Case C-377/98 Netherlands v Parliament and Council (par. 71 and 76), and reiterated by the CJEU in Case C-34/10 (par. 33-34).

In conclusion, considering the term "uses" of human embryos for industrial or commercial purposes" in Article 6(2)b, only a broad and comprehensive interpretation of what constitutes "use" is in accordance both with the legal provisions and with the spirit, intentions, and will-formation of the European legislator. Reducing the term "uses" of human embryos to "non-destructive" uses only, as suggested in the *Report*, is not a justified means of interpretation.

5. Scientific validation: Chung 2008 does not provide sound evidence for "non-destructive" use of human embryos

In addition, several counter-arguments can be made with respect to some scientific arguments raised in the *Report*. The methods described in Figure 1 of the *Report* are misleading insofar as the figure might suggest that ANT (Altered Nuclear Transfer**)**, SBB (Single Blastomere Biopsy), and "organismically dead" embryos would be on an equal footing with "classical" (hESC) or "reprogramming" (iPS) methods.

It can and should not be deduced from this figure that ANT and SBB are standard scientific practices which provide methods for producing pluripotent stem cells without the need to destroy the human embryo. ANT, SBB, and "arrested embryos" have been proposed and

[10] Cited from the EPO, Edinburgh Case, Grounds for the decision, Application No. 94913174.2, 21.07.2003, p. 22.

[11] Article 6(2)c was introduced as amendment 55 by the European Parliament and held as unpatentable "methods in which human embryos are used". After acceptance by the Commission, this wording was changed in the Common Position adopted by the Council to "uses of human embryos for industrial and commercial purposes" For references, see Comments of the President of the EPO on G2/06, 2006, pp. 38-39).

pursued by some researchers in order to overcome funding restrictions in the US and patent restrictions in Europe. However, those methods are highly controversial among researchers themselves, as they are fraught with scientific, logistical, medical, and ethical problems.[12] They have not been applied widely, and belong neither to standard practices in the lab nor have they ever, to our knowledge, been used in clinical practice.

In particular, it is inappropriate to use the method published by Chung et al. in 2008 as a loophole to allow patentability of methods and products "indirectly" derived from human embryonic stem cell lines for patents which were filed after 10 January 2008. Such a granting practice has been applied by the European Patent Office (EPO) and has been consented to by the majority of the members of the Commission's Expert Group in the *Report (Chapter* 5.3.2.1), arguing that such inventions could be based upon the derivation method disclosed by Chung et al. in 2008. Chungs' publication claims to have enabled the provision of hES lines without destroying a human embryo in any production step for the first time.[13] It is based on one single cell line (No. 5) said to be produced from a single blastomere, without co-culture with hESC.

However, the belief that Chung's method indeed changed the field of human embryonic stem cell research must be contested. The most relevant reasons for contestation are:

1) The existence of the cell line in question (No. 5 in Chung et al. 2008) is questionable, as it is not available to international researchers and no published studies are listed that utilise this cell line.
2) The method has no real world applicability with respect to the transfer of the remaining embryo (from which a single blastomere was extracted) to a woman's uterus. All biopsied embryos used by Chung et al. 2008 were frozen (cryopreserved) but never implanted.
3) The method applied in practice – taking a blastomere from a human embryo without destroying it – could cause harm to the embryo, without any indication and medical benefit for the embryo itself (hence, Recital 42 of Dir. 98/44 does not apply).
4) The blastomere taken from an embryo at the eight cell stage may still be considered totipotent.[14]

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[12] Byrnes for instance states that ANT "as currently conceived, cannot realistically work": Byrnes WM 2007: The flawed scientific basis of the altered nuclear transfer-oocyte assisted reprogramming (ANT-OAR) proposal. Stem Cell Rev. 3(1): 60-65. For other objections see: Bobbert M 2006: Ethical questions concerning research on human embryos, embryonic stem cells and chimeras. Biotechnol J. 1(12):1352-69.

13 Chung Y. et al.: Human Embryonic Stem Cells Lines Generated without Embryo Destruction. Cell Stem Cell 2008 2(2) 113-117, (published online 10 January 2008).

14 *Totipotent cells* are mentioned in the exclusions from patentability in Recital 38 of Directive 98/44/EC. In some national legislations, e.g. Germany, embryo is defined as any human totipotent cell which, exposed to the necessary conditions, has the potential to divide and develop into an individual (2002 Stem Cell Act, §3 (4). There are different scientific definitions concepts of totipotency. It is agreed that blastomeres from the 2 to 4 cell stages are totipotent (See Geens et al. 2009: Human embryonic stem cell lines derived from single blastomeres of two 4-cell stage embryos, Human Reproduction, Vol. 24, No.11 pp. 2709–271.). According to scientific reviews of the state of the knowledge to date, totipotency can also not be excluded for blastomeres from the 6 or 8 cell stage because cleavage does not happen for all blastomeres simultaneously. For legal and ethical reasons, single blastomeres or manipulated human embryos are not transferred into a uterus to test their potency, and thus totipotency will never scientifically be proved in the human. (De Paepe C, Krivega M, Cauffman G, Geens M, Van de Velde H. 2014: Totipotency and lineage segregation in the human embryo. Mol Hum Reprod. 2014, Jul;20(7):599-618, p. 602).

Therefore, two members of the Expert Group have drawn the conclusion that a single blastomere in the 8 cell stage, as used by Chung et al. 2008, has to be legally treated as totipotent. In their reasoning, as it is about human embryos, it is prudent to err on the side of caution. Such a position is also backed by the view of

5) On the basis of information currently available, to date no stem cell lines produced by this method are used in human embryonic stem cell research for therapeutic purposes.

In conclusion, the EPO appears to be using this method as a legal artefact without sufficient technical basis. One single cell line in a single publication does not provide sufficient and robust scientific evidence to legitimise such a far-reaching shift in patentability which has effects on several hundred pending human embryonic stem cell applications filed after 10 January 2008 (compare Table 1). Moreover, patents granted on the basis of this method would give adverse incentives to the field of stem cell research as it would encourage such methods fraught with medical and ethical problems. Alternative strategies which do not require human embryos at all, such as iPS cells, and further strategies which are based on "direct reprogramming" by "direct conversion" of human cells, and thus are "bypassing pluripotency", will be more conducive for stem cell research, especially as recent research indicates that human pluripotent stem cells "*in vitro* can form structures that have some resemblance to embryos" post implantation.[15]

In conclusion, it amounts to a violation of the will of the European legislator to bypass non-patentability of "uses of human embryos" (Art.6(2)c) by theoretical and technical means which are not based on sound, evidence-based science and real world applicability. Therefore, the Chung et al. 2008 technology is not an adequate means for allowing the granting of patents on inventions derived from human embryonic stem cells.

6. Parthenotes as stem cell source: not identical with embryonic stem cells

In the EPO's recent revision of the Guidelines for Examination, valid from 1 November 2015, and following the CJEU ruling in C-364/13, the EPO refers to the "state of the art at the date of filing" (see Annex 4 in the *Report*). As explained in the Report, "the EPO now considers inventions relating to human pluripotent stem cells *including hES cells, to their uses and to products derived from them as patentable* from 5 June 2003 on" (*Report* page 22, Emphasis added).[16] Accordingly, the EPO's new first-instance practice, adopted around October 2015, takes 5 June 2003 as new cut-off date, based on WO 03/046141 (*Report,* page 15). [17]

Indeed, the PCT application WO 03/046141 (Advanced Cell Technology) discloses in Example 4 a protocol for the "Production of Autologous Cells by Parthenogenetic Activation of Oocytes" (pp. 45-46). However, the resulting cells are human parthenogenetic embryonic stem cells (hpES), which are deemed "ES-like cells" (p. 47). Therefore, even though these

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experimental animal studies in mice and rabbits, which have provided strong indications for totipotency of at least some of the blastomeres even in the 16 cell stage embryo (Ziomek et al. 1982, Chisholm/Fleming et al. 1984 and further references cited in: T. Littwin/ H. -W. Denker 2011: Segregation during cleavage in the mammalian embryo? Histochem Cell Biol (2011) 135:553–570).

[15] See: Pera Martin F et al. 2015:What if stem cells turn into embryos in a dish? in: Nature methods, vol. 12 (10) 2015: 917-919; also already Denker, Hans-Werner 2012: Time to Reconsider Stem Cell Induction Strategies. Review, in: Cells 2012, 1, 1293-1312.

[16] See end of Chapter 5.3.2.1, Chapter 5.2.2., and Annex 4 in the *Report.*

[17] This practice is, as always is the case, to be considered as preliminary and subject to review by the EPO's Boards of Appeal. As yet, it has not yet been confirmed by Case Law. The EPO Boards of Appeal's latest decision on this matter, T 1808/13, considered 2007 as the cut-off date for stem cells derived from parthenogenetic embryos (referring to Documents D23 and D21).

hpES cells are *similar* to human embryonic stem cells (hESC), they are *not identical* to hESC. Such a conclusion is scientifically inadmissible.[18]

Activated human eggs called parthenotes do not involve the union of male and female germ cells, and so genetic material will be derived exclusively from the female oocyte donor.[19] Therefore, they have important biological differences to fertilised human embryos.[20] Even though "pESC are similar to ESCs", they lack paternal imprinted genes.[21] This is one of the reasons why parthenotes normally do not develop into full human beings.[22]

Moreover, the conclusion drawn by the EPO from the CJEU judgment in C-364/13 is wrong. The CJEU was only asked whether parthenotes were included in the term "human embryos" in Article 6(2)(c) of Directive 98/44/EC. The CJEU responded that

> "Article 6(2)(c) (...) must be interpreted as meaning that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo', within the meaning of that provision, if, in the light of current scientific knowledge, it does not, in itself, have the inherent capacity of developing into a human being, this being a matter for the national court to determine."

Hence, the court neither took a decision as to whether parthenotes are eligible for patent nor whether processes to obtain parthenogenetic embryonic stem (hpES) derived from parthenotes are patentable. Parthenotes may fall under the exclusions in Art. 5 and Art. 6(1) of Directive 98/44/EC.

But even if these aforementioned products and processes were patentable, we consider the conclusion drawn by the EPO that human embryonic stem cells (hESC), their uses, and the products derived from them are patentable to be incorrect, because hpES are not identical to hESCs.

Moreover, we would like to draw attention to the fact that the literature has described cases which demonstrate the ability to produce the birth of live parthenogenetic mice which were able to produce offspring when the appropriate imprinting of key genes by a maternal genome were expressed.[23] In humans, this concept was also demonstrated in a single case report of spontaneous parthenogenetic chimerism in which the patient survived with a mixed makeup of normal and parthenogenetic cells.[24] Therefore, the question as to whether

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[18] Swelstad BB, Kerr CL 2009: Current protocols in the generation of pluripotent stem cells: theoretical, methodological and clinical considerations, in: Stem Cells Cloning 22(3):13-27.

[19] Cibelli JB, Cunniff K, Vrana KE. 2006: Embryonic stem cells from parthenotes, in: Methods Enzymol. 418: 117-35; Kim K, Ng K, Rugg-Gunn P, et al. 2007: Recombination Signatures Distinguish Embryonic Stem Cells Derived by Parthenogenesis and Somatic Cell Nuclear Transfer. Cell Stem Cell 1:346-352.

[20] Brevini TA/ Gandolfi F. 2008: Parthenotes as a source of embryonic stem cells, in: Cell Proliferation 41 Suppl 1: 20-30.

[21] Daughtry B/ Mitalipov S. 2014: Concise review: parthenote stem cells for regenerative medicine: genetic, epigenetic, and developmental features, in: Stem Cells Translational Medicine 3(3): 290-298.

[22] Wu Q, Kumagai T, Kawahara M, Ogawa H, Hiura H, Obata Y, Takano R, Kono T. 2006: Regulated expression of two sets of paternally imprinted genes is necessary for mouse parthenogenetic development to term, in: Reproduction. 131(3): 481-488.

[23] Kono T/ Obata Y/ Wu Q et al. 2004: Birth of parthenogenetic mice that can develop to adulthood, in: Nature.;428 (6985): 860–864; Loebel, David A. F. / Tam, Patrick P. L. 2004: Genomic imprinting: Mice without a father, in: Nature 428, 809-811; Wu Q, Kumagai T, Kawahara M, et al. 2006: Regulated expression of two sets of paternally imprinted genes is necessary for mouse parthenogenetic development to term, in: Reproduction 131(3): 481–488.

[24] Strain L/ Warner JP/ Johnston T/ Bonthron DT. 1995: A human parthenogenetic chimaera, in: Nature Genetics 11(2): 164–169. Also cited in Swelstad BB, Kerr CL 2009: Current protocols in the generation of

human parthenotes in itself have the inherent capacity of developing into a human being has not yet conclusively been answered in scientific knowledge.

7. The creation of artificial gametes and embryos must remain exempted from patentability

In Chapter 5.2.2., the *Report* correctly states:

> "Other new methods, like the artificial creation of human germ cells may also become available that could lead to artificial creation of human embryo-like entities. Inventions related to such methods or their products would be excluded from patentability. If these entities fulfil the definition used by the European Court of Justice of being “inherently” “capable of developing into of a human being”, they would have to be considered “human embryos”. New methods which could potentially lead to the creation of artificial germ cells or germ cell lines are excluded as such from patentability according to Article 5 and Recital 16 of the directive. Additionally, inventions involving an embryo produced by means of artificial germ cells should be treated in the same way as any inventions related to a 'natural' embryo produced by the fusion of an oocyte and a sperm cell."

However, the *Report* does not make sufficiently clear that the term "uses of human embryos" in Article 6(2)c" may also extend to uses of human embryos in which an embryo is being technically created. It is important to take recent developments of such possible "constructive uses" of human embryos into account. The term "constructive use" comprises the creation of an artificial embryo by means other than normal in-vitro fertilisation (IVF). One example for such a new method for the construction of an embryo is "mitochondria replacement", also termed "three-parent babies".[25]

Another novel method for the construction of an embryo by new means is to use iPS or embryonic stem cells to create artificial gametes and embryos. Using their own genetic material, the latter technology might allow same-sex-partners (e.g. two males) to create an embryo that is genetically related to both partners. It might also allow one individual to reproduce without another genetic parent by conjoining artificially created male and female germ cells from a single individual.[26]

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pluripotent stem cells: theoretical, methodological and clinical considerations, in: Stem Cells Cloning 22(3):13-27 on p. 20.

25 In "mitochondria replacement", also termed "three-person in vitro fertilisation', an embryo with genetic material from three different people (two females and one male) is created, which also results in inheritable genetic modification (changes that would be passed on to future generations). Some observers have warned that this would open the door for human germline modification. (Darnovsky, Marcy 2013: A slippery slope to human germline modification. The United Kingdom’s decision to trial the technique of mitochondrial replacement is premature and ill-conceived. Nature 499, 127, 11 July 2013).

26 For the scientific background, see the report of the German Ethics Council: "Scientists have already been successful in developing germ line cells from iPS cells and cultivating them into fully functional germ cells following implantation in the gonads of animals. In animal experiments, sperm and egg cells artificially produced from such iPS cells have, through fertilization, lead to the creation of viable mice. It cannot be ruled out that, in future, this technology could be applied to human reproduction in constellations where procreation by natural means is impossible. Same-sex couples could, for example, produce children that are genetically related to both parents. The method could even be used to combine artificially created male and female germ cells generated from the same individual, resulting in an embryo. This raises an issue that is at least related to concerns regarding cloning: although the embryo is not a clone, it has only one genetic parent." (See for references: "Ethics Council sees need for clarification regarding artificially created germ cells and embryos" 15.09.2014, p.4, http://www.ethikrat.org/files/recommendation-stem-cell-research.pdf. It should be noted that a review article in 2000 already noted as a conclusion "Alternative sources of gametes are not merely

In light of these recent developments, it is recommended that both the European Commission and the EPO specify and clarify that the term “germ cell” (Directive 98/44/EC, Recital 16) applies not only to naturally created egg and sperm cells, but also includes artificially created egg and sperm cells (for example from iPS cells).

For the time being, the EPO's interpretation of patent exclusions related to germ cells appears to be as follows: The Guidelines for Examination in the EPO explicitly state in G-II, 5.3 that according to Rule 29(1) EPC, the human body, at the various stages of its formation and development, [...], cannot constitute patentable inventions. Such stages in the formation or development of the human body include germ cells (Directive 98/44/EC, Recital 16). It follows that human germ cells, be they artificially created or naturally occurring, are plainly unpatentable under the EPC. Germ cells are mentioned in Recitals 16 and 38[27], which have an impact on the interpretation of Articles 5 and 6. Germ cells, in particular oocytes, are relevant inter alia in the above mentioned use of parthenotes as a source of human embryonic stem cells and in SCNT techniques, where the resulting cloned embryo could be used for the derivation of human embryonic stem cells. SCNT, being a process for cloning human beings, is explicitly excluded from patentability under Rule 28(a) EPC. It is worth noting that, according to the Guidelines for Examination in the EPO, G-II, 5.3, for the purpose of this exception, a process for the cloning of human beings may be defined as any process, [...], designed to create a human being with the same nuclear genetic information as another [...] human being (EU Dir. 98/44/EC, rec. 41). However, that conjoining of artificially created male and female germ cells from a single individual is functionally equivalent to a (cloned) human embryo would require scientific and legal clarification.

In any event, such methods for producing artificial embryos and the resulting entity itself should not be eligible for patentability, either under either Article 6(2)a/ Rule 28(a) EPC (cloning), under Article 6(2)b /Rule 28(b) EPC (modification of the germ line genetic identity of human beings), under Article 5(1)/ Rule 29(1) EPC (the human body at the various stages of its formation and development), or ultimately under Article 6(1)/ Art. 53(a) EPC. It is necessary for both the European Commission and the EPO to specify and clarify that such methods and products would fall under the prohibitions of Articles 5 and 6 of the Directive 98/44/EC.

Here again, it is necessary to stress that such a provision of non-patent eligibility would not ban respective research, but would remove some commercial incentives for such research and development. As patents are granted according to the "winner-take-all" principle, only the first inventor who has filed the patent gets the temporary exclusivity. Hence, patents can have an accelerating effect on spurring such new techniques. Democracy, however, needs time to deliberate whether such new forms of procreation should be made available or not.

Proceeding with caution and without patents as an incentive for the construction of artificial gametes and embryos will allow European society sufficient time to debate whether such developments are socially desirable or not and whether national legislation of such

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science fiction, but already are a concrete fact." (Tsai et al. 2000: Alternative sources of gametes: reality or science fiction? Human Reproduction 15(5):988-98, p. 995).

[27] Recital 38 refers to processes to produce chimeras from germ cells or totipotent cells of humans and animals, which are excluded from patentability under Art. 53(a) EPC. A narrow interpretation of this wording suggests that totipotent cells are only excluded when used for chimeras. A broad interpretation means that totipotent cells are excluded anyway. The author follows the second interpretation, as totipotent cells are equivalent to a human embryo, which is excluded in Article 5(1)/ Rule 29(1) EPC.

developments should be set on the agenda. Granting patents on such inventions for creating artificial gametes and embryos would set both an incentive for pursuing such research and an unfavourable precedence for other areas of law.

Moreover, it is important to state that any use of human egg cells for third parties and/or non-procreative purposes, for instance for parthenotes or for SCNT as sources of human embryonic stem cells, also carries the risk for women to be exploited as oocyte providers. The 2005 UN Declaration on Human Cloning (59/280) called upon the nations "to prohibit all forms of human cloning", both reproductive cloning and research cloning (SCNT). It also called upon Member States "to take measures to prevent the exploitation of women in the application of life sciences". [28] This call was reiterated in a resolution of the European Parliament.[29]

In conclusion, "constructive uses" of human embryos and gametes, by the creation of artificial gametes from stem cells, and by the conjoining of such artificial germ cells to a totipotent cell must remain exempted from patentability. Such techniques increase the risks of inducing and transmitting serious harms to the embryo and developing human being. Such techniques also presuppose that women provide a vast amount of oocytes for enucleation and/or act as surrogates to carry the artificially created embryo to term. Hence, they rely on the instrumentalisation of women and violate their dignity. For cross-compliance and cross-coherence of law, it is important that patent law adheres to higher ranking legal norms such as the wellbeing of the child-to-be and the dignity of women.

8. CRISPR must not be patentable for human germline modification

In Chapter 5.1., the *Report* correctly states: "Equally excluded from patentability are processes for cloning human beings; and claims to the processes for modifying the germ line genetic identity of human beings (Article 6 (2) a) and b))." In the corresponding footnote 17, it rightly refers to "recent genome editing technologies in pluripotent and other stem cells and in early stages of human development". However, the *Report* fails to elaborate on these new genome editing technologies and the scientific and legal debate associated with it, as one would expect in such a *Report* on the scientific developments and implications (Art. 16 (c) of Directive 98/44/EC).

It must be noted that recent scientific advances in genome editing have received high attention in science, policy, and the public. CRISPR-Cas9 and CRISPR-Cpf1 (Clustered Regularly Interspaced Short Palindromic Repeats) promise precise, fast, inexpensive, and easy to handle ways of genome editing and can be employed in all kinds of DNA. These and other genome editing techniques such as Zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and oligonucleotid directed mutagenesis (ODM)[30] have been hailed as revolutionary with significant advantages for research and therapeutics

28 United Nations Declaration on Human Cloning (59/280). Resolution adopted by the General Assembly at its 82nd meeting, on 8 March 2005. <http://www.un.org/law/cloning/

29 European Parliament 2005: Planned egg cell trade. Resolution on the trade in human egg cells. P6_TA(2005)0074; http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2005-0074+0+DOC+XML+V0//EN. See in particular Numbers 9-13.

[30] Church, G., Regis, E. 2012: Regenesis. How synthetic biology will reinvent nature and ourselves. Basis Books: New York; Gaj, Thomas et al. 2013: ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. Review, in: Trends in Biotechnology, 31(7): 397-405.

as well as for economics and intellectual property[31] However, if genome editing techniques such as CRISPR were applied in heritable germline modification, they could have an unpredictable effect on future generations. Hopes and fears are not only present in media and policy debates, but also among researchers themselves. On the cautious pole of the spectre, scientists in Europe and the US have called for a moratorium and a public debate on CRISPR in the human germline.[32] On the other pole, researchers in China have conducted first experiments in using CRISPR for editing the genomes of nonviable human embryos.[33] UK funders have signalled support for germline-editing research,[34] and parts of the international scientific community, such as the Hinxton Group, have recommended that editing of the human genome in embryos should be allowed for basic research and suggested that the door should not be totally closed towards allowing genetic engineering of humans in the future. .[35]

Ledford, who mentions around 200 patent applications worldwide, recognises that "a patent battle" has intensified with a sharp increase in patent filings in 2014.[36] Kupecz refers to anonymous 'third-party observations' filed at the EPO aimed at preventing the granting of a European patent.[37] For Europe, our own tentative research has revealed more than 150 patent applications at the European Patent Office and 50 patents granted, of which were four granted to the US Broad Institute of MIT and Harvard and its member Feng Zhang. Some of the patents granted include the disclaimer "not for human germ line".

The potential for using this technology in germ cells and embryos, or in stem cells which were later introduced in enucleated oocytes (SCNT), has definitely reignited the debate on human germline interventions. At present, however, human germline editing on human embryos in the clinical context is prohibited in more than 40 countries worldwide, including 14 European states.[38]International and European regulations also consider human germline modification as unethical human experimentation or as abuse of human rights. [39]

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[31] Ledford, Heidi 2015: CRISPR, the disruptor. A powerful gene-editing technology is the biggest game changer to hit biology since PCR. But with its huge potential come pressing concerns, in: Nature 522: 20-24.

[32] Baltimore, D. et al. 2015: A prudent path forward for genomic engineering and germline gene modification, Science 348: 36-38; Lanphier, Edward/ Urnov, Fyodor et al. 2015: Don't edit the human germ line, in: Nature 519(7544): 410 – 411; Leopoldina 2015: The opportunities and limits of genome editing. Leopoldina, acatech and Union of the German Academies of Science, Statement, September 2015, available at: http://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/2015/stellungnahme_genome_editing_2015.pdf); BBAW (Berlin-Brandenburg Academy of Sciences and Humanities) 2015: Human genome surgery – towards a responsible evaluation of a new technology, available at: www.gentechnologiebericht.de/bilder/BBAW_Human- Genome-Surgery_PDF-A1b-1.pdf.

[33] Liang, Puping/ Yanwen, Xu et al. 2015: CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes, in: Protein and Cell 6(5): 363–372; Cyranoski, David/ Reardon, Sara 2015: Chinese scientists genetically modify human embryos. Rumours of germline modification prove true — and look set to reignite an ethical debate, in: Nature, April 22, 2015.

[34] Joint statement of UK science bodies 2015: Genome editing in human cells – initial joint statement", available at: http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Genome-editing/WTP059704.htm; Sample, Ian 2015: GM embryos: time to decide, say scientists, The Guardian, 2 September 2015, p.1-2.

[35] Hinxton Group 2015: Statement on Genome Editing Technologies and Human Germline genetic Modification, available at: http://www.hinxtongroup.org/hinxton2015_statement.pdf

[36] Ledford, Heidi 2015: CRISPR, the disruptor, in: Nature 522, June 04, 2015: 20-24.

[37] Kupecz, András 2014: Who owns CRISPR-Cas9 in Europe? in: Nature Biotechnology 32(12): 1194–1196.

[38] Ishii, Tetsuya/ Araki, Motoko 2014: International regulatory landscape and integration of corrective genome editing into in vitro fertilization, in: Reproductive Biology and Endocrinology 12(108),

[39] The UNESCO's Universal Declaration on the Human Genome and Human Rights indicates in Article 24 that "germline interventions" could be "contrary to human dignity." The Council of Europe's Convention on Human Rights and Biomedicine indicates in Article 13 that "an intervention seeking to modify the human genome may

Article 6(2) (b) of Directive 98/44/EC excludes patentability for "processes for modifying the germ line genetic identity of human beings". However, at the international level, there is no legal consensus as to whether human embryos are to be defined either as "human beings" or as "human life", with the latter implying less legal protection.

The European Court of Human Rights in VO v. France, and referring to the Oviedo Convention on Human Rights and Biomedicine, also observed that at European level,

> "there is no consensus on the nature and status of the embryo and/or foetus. (...) At best, it may be regarded as common ground between States that the embryo/foetus belongs to the human race. The potentiality of that being and its capacity to become a person – enjoying protection under the civil law (...) require protection in the name of human dignity, without making it a “person” with the “right to life” for the purposes of Article 2."[40]

Therefore, it is paramount that both the European Commission and the EPO specify and clarify that Articles 6(2)b and 6(2)c, which exclude patentability of human germline modification and the use of human embryos for commercial and industrial purposes, apply to CRISPR-Cas9 and CRISPR-Cpf1 if practiced in human germ cells and human embryos. Only such clarifications will ensure that patents do not serve as incentives to pursue such controversial research which is contrary to European values, *ordre public*, and public policy.

10. Conclusions

More public debate, deliberations in the European Parliament and the Council, and inclusion of civil society organisations is needed in determining the appropriate interpretation of Directive 98/44/EC. At present, the discussion is often confined to patent attorneys, patent lawyers, and public servants of patent offices, and thus often restricts reasoning to formalistic legal arguments. The Expert Group could have been an opportunity for a broad deliberation following Habermasian standards on discourse. Unfortunately, it has not used this opportunity, as arguments and validity claims brought forward in many instances were not refuted by reasoned argumentation but just cut off by the power of majority votes. Furthermore, the European Patent Office's granting practice and governance structures lack transparency and accountability to the citizens of Europe, an issue which needs to be addressed in current patent reforms. More transparency and an overhaul of its governance structure would be welcomed both by the national and European legislators and by the general public. It would also be in line with the EPO's public mission and with the principle of disclosure, which is one of the fundaments of patents' legitimacy. Transparency and accountability of the EPO would first require providing data on the stem cell patent applications filed and granted, and second, for the EPO's granting practices on human embryonic stem cells, revealing the scientific and legal rationales of the EPO's new interpretation of the EPC's Article 53(a) and Rule 28 with reference to Chang et al. 2008 and PCT application WO 03/046141 in the EPO's Guidelines for Examination.

Moreover, the European Patent system urgently needs to be democratised to serve the public interest and to comply with the social contract upon which it is constituted. A broader view on both the empirics and impact of patents is needed which recognises that patents are embedded in social and economic contexts; therefore, interpretation of legal statutes must

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only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.”

40 European Court of Human Rights, Case of VO v. France, Application no. 53924/00, 08.07.2004, Point 84. p. 38.)

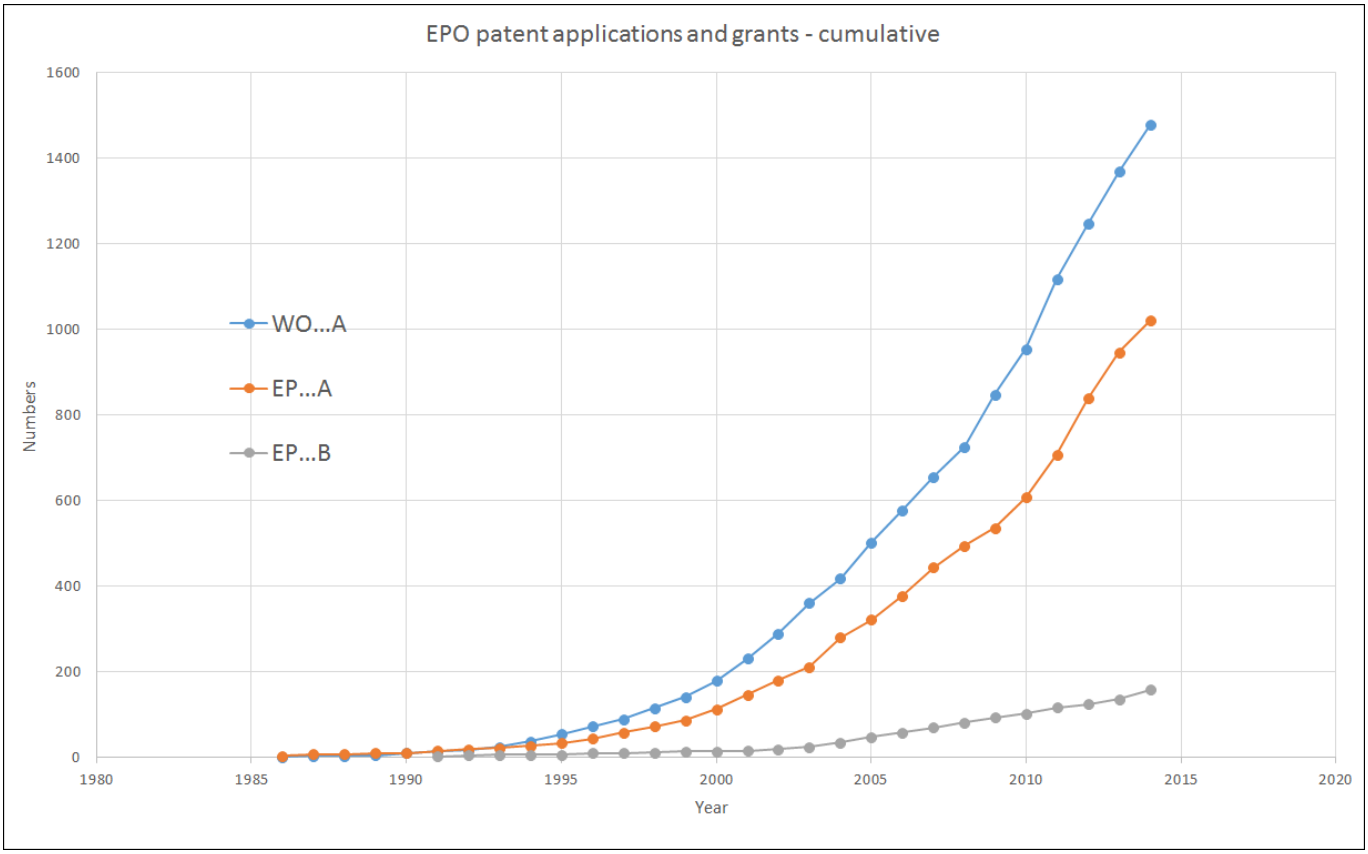
not be confined to a literal interpretation, but must also include the history and the purpose of the EU Biotech Patent Directive as well as the context of development and implications in its application.

There is a strong need for a better balance to secure the proper interpretation of the *ordre public* and morality exemption in European patent law in accordance with the purposes and intentions of the European legislator and with the EU's Charter of Fundamental Rights. This requires the European Commission to take the initiative in strengthening the patent exclusions in Articles 5 and 6.

The first step to be taken by the European Commission should be to provide adequate clarification and precise guidance for the correct interpretation of the EU Biotech Patent Directive, as indicated in this dissenting opinion. These clarifications would establish new, binding rules for the interpretation of current patent law without changing the text of the Directive 98/44/EC. As a fall-back position, a further step could be a separate legislative action without altering the Directive as such. Another step, and a last fall-back position in case the former provisions were unsuccessful, would be legislative action that may include a thorough revision of the EU Biotech Patent Directive in order to incorporate robust and legally defined limits of patentability. Contrary to the views expressed in the majority opinion of the Expert Group, taking no political action is not and cannot be an option.

ANNEX

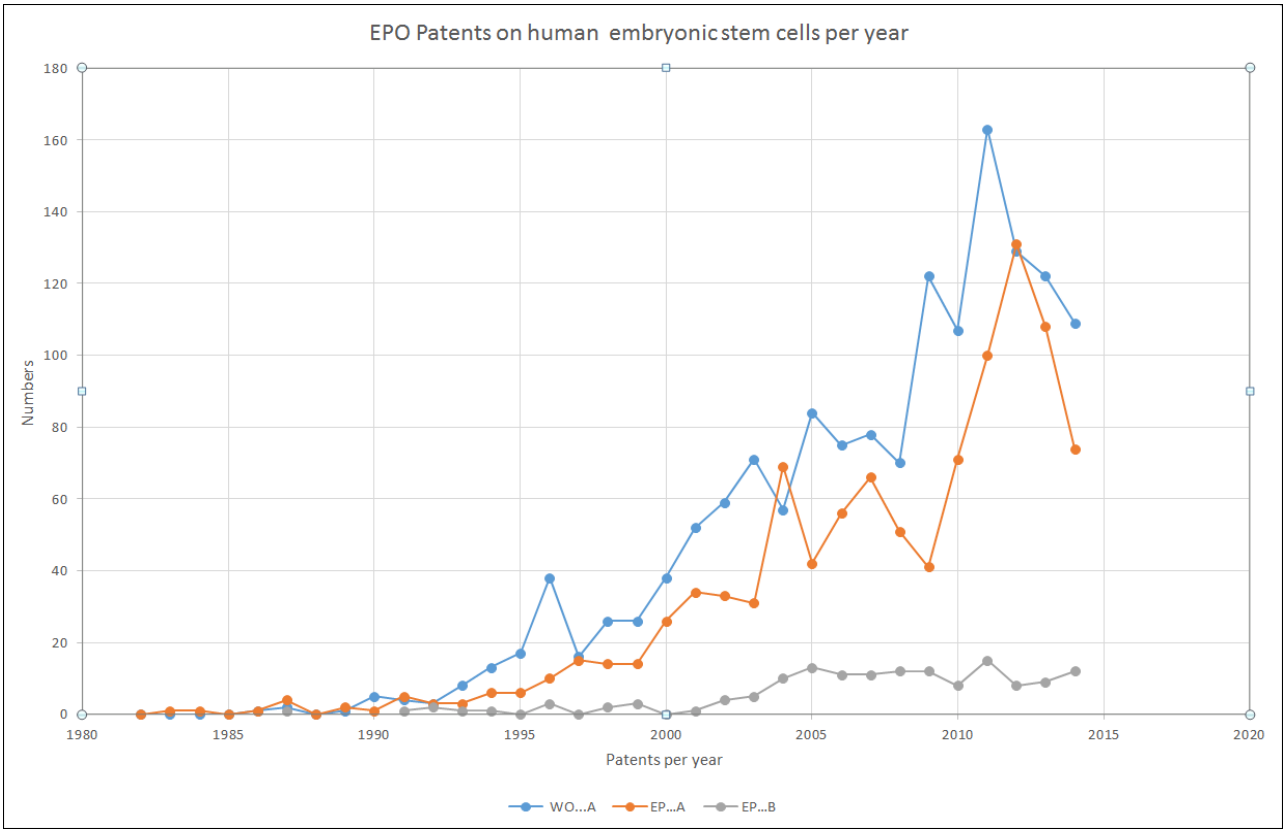
Table 1:
EPO Patent applications and grants on human embryonic stem cells (1986-2014, cumulative)



Source: Global Patent Index
(Mainly based on classification IPC=C12N0005 and English title or abstract = embryonic or pluripotent or totipotent)

WO...A = PCT Applications
EP...A = European Applications
EP...B = Granted European Patents

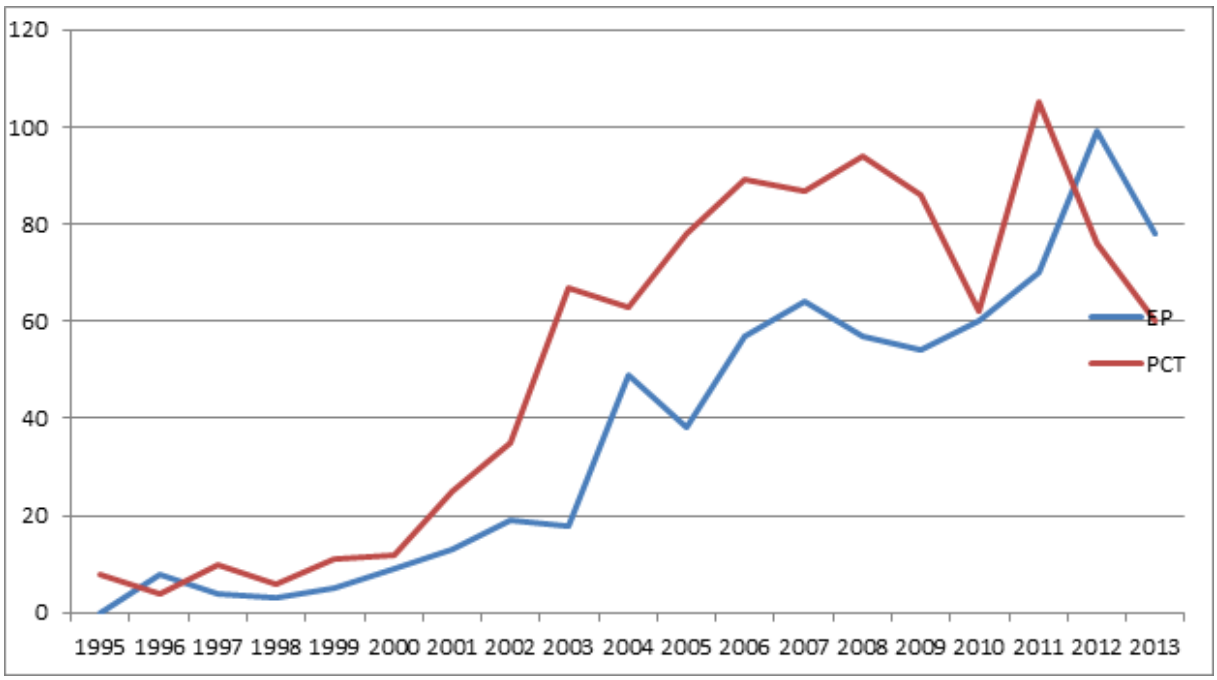
Table 2: EPO Patent applications and grants on human embryonic stem cells (1986-2014, per year)



Source: Global Patent Index
(Mainly based on classification IPC=C12N0005 and English title or abstract = embryonic or pluripotent or totipotent)

WO...A = PCT Applications
EP...A = European Applications
EP...B = Granted European Patents

Table 3: Number of published embryonic stem cell patent applications per year (1995-2013), as provided by source EPO



Source: European Patent Office, based on manual sorting of cases.

This statistics had formed part of the draft report of the expert group but was removed because the majority considered that the value of any statistics is limited, as they are all inexact.