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WAYS OUT OF THE PATENTING PROHIBITION? HUMAN PARTHENOGENETIC AND INDUCED PLURIPOTENT STEM CELLS

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ABSTRACT

According to the judgement of the European Court of Justice in 2014, human parthenogenetic stem cells are excluded from the patenting prohibition of procedures based on hESC by the European Biopatent Directive, because human parthenotes are not human embryos. This article is based on the thesis that in light of the technological advances in the field of stem cell research, the attribution of the term 'human embryo' to certain entities on a descriptive level as well as the attribution of a normative protection status to certain entities based on the criterion of totipotency, are becoming increasingly unclear. The example of human parthenotes in particular demonstrates that totipotency is not at all a necessary condition for the attribution of the term 'human embryo'. Furthermore, the example of hiPSC and somatic cells particularly shows that totipotency is also not a sufficient condition for the attribution of a normative protection status to certain entities. Therefore, it is not a suitable criterion for distinguishing between human embryos worthy of protection and human non-embryos not worthy of protection. Consequently, this conclusion has repercussions for the patenting question. The strict delineation between an ethically problematic commercial use of human embryos and the concomitant patenting prohibition of hESC-based procedures and an ethically unproblematic commercial use of human non-embryos and the therefore either unrestrictedly permitted (cf. human parthenotes) or even unregulated (cf. hiPSC) patenting of procedures based on these alleged alternatives becomes increasingly blurred.

INTRODUCTION

According to the decisions of the European Court of Justice (ECJ) in 2011 and the German Federal Court of Justice (FCJ) in 2012, procedures based on human embryonic stem cells (hESC) are excluded from patentability if they require 'the prior destruction of human embryos or their use as base material, whatever the stage at which that takes place'.[1] These rulings are based on the interpretation of art. 6 of the European directive on the legal protection of biotechnological inventions, according to which 'inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality' (art. 6 para. 1 98/44/EC), particularly, 'uses of human embryos for industrial or commercial purposes' (art. 6 para. 2c 98/44/EC). In its reasoning, the ECJ pointed out that the context and aim of the biopatent directive shows 'that the European Union legislature intended to exclude any possibility of patentability where respect for *human dignity* could thereby be affected'.[2] Correspondingly, according to the justification of the FCJ, unrestricted permission of the patent in question would create the impression that the German government approves treatments of human embryos which violate *human dignity*.[3]

[1] ECJ C-34/10, 18 Oct 2011, recital 52.

[2] Ibid: recital 34.

[3] Cf. German FCJ X ZR 58/07, 27 Nov 2012, recital 19.

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The decisions of both rulings are based on two normative assumptions: A) human embryos have human dignity, B) the destruction of human embryos for commercial purposes violates their human dignity. Curiously, none of these two assumptions refer to reasons that are immanent to patents and derived from their meaning or function – as for example the scope of a patent (especially with regards to absolute product protection) or the distinction between discovery and invention (especially with regards to gene patents). Instead they refer to the origin of hESC: i.e. human embryos. Not human embryos, but *hESC* are the actual objects of commercialization and neither human embryos nor hESC as such, but *procedures* based on hESC are the actual objects of patenting. Thereby, the rulings circumvent the question regarding the normative status of hESC and refer back to the supposedly more clearly determinable normative status of human embryos. Therefore, the patenting prohibition depends on the definition of the term '*human embryo'*, which refers to the capacity of an entity to develop into a (born) human being (totipotency). Following this reasoning, the patenting of procedures based on human pluripotent stem cells that are not derived from human embryos (or that function without the destruction of human embryos) is permitted.

Among the presumably ethically sound alternatives to hESC derived from human embryos that have been gaining importance since their independent development in 2007, human parthenogenetic stem cells (hpSC) derived from human parthenotes[4] and human induced pluripotent stem cells (hiPSC) reprogrammed from human somatic cells[5] are considered.[6] The difficulties of attributing totipotency to a certain entity is illustrated by the two opposing decisions of the ECJ on the question of whether human parthenotes are human embryos or not. The ECJ decided in 2011, that the definition of the term 'human embryo' within the meaning of art. 6 of the Biopatent Directive 'must be understood in a wide sense'.[7] This wide sense includes not only entities created by fertilization, but also by somatic cell nuclear transfer (SCNT) and parthenogenesis, as they are also 'capable of commencing the process of development of a human being'.[8] But in 2014 the ECJ revised its earlier decision since 'the mere fact that [an] organism commences a process of development is not sufficient for it to be regarded as a human embryo' within the meaning of the Biopatent Directive.[9] Decisive for the definition of the term 'human embryo' would rather be an 'inherent capacity of developing into a human being'.[10] This capacity would not apply to a human parthenote *in itself*[11] as it 'develop[s] only to the blastocyst stage'.[12]

This article will analyse the descriptive and normative delimitability of human parthenotes and hiPSC from human embryos and hESC against the backdrop of the recent ECJ decision regarding the patentability of hpSC. The examination is based on the thesis that in light of the technological advances in the field of stem cell research, both the attribution of the term 'human embryo' to certain entities on a descriptive level (see Table 1, first questionable assumption: Human parthenotes are not human embryos) and the attribution of a normative protection status to certain entities (see Table 1, second questionable assumption: HiPSC are not totipotent) on the basis of the criterion of *totipotency,* are becoming increasingly unclear. In Section 1, it will be shown with the example of human parthenotes that totipotency is not at all a necessary condition for the attribution of the term 'human embryo'. Furthermore, in Section 2, the example of hiPSC will be used to show that it is also not a sufficient condition for the attribution of a normative protection status to certain entities. Thus, it is not a suitable criterion for distinguishing between human embryos worthy of protection and human non-embryos not worthy of protection. The blurred line between a human embryo and (supposedly) distinct entities such as human parthenotes or cells such as hiPSC and hpSC questions whether these alternatives to hESC are in fact alternatives. As such, the uncertain status of these supposed alternatives to hESC has repercussions for the patenting question. The strict delineation between an ethically problematic commercial use of human embryos, with the concomitant patenting prohibition of hESC-based procedures and an ethically unproblematic commercial use of human non-embryos, and with, therefore, either unrestrictedly permitted (cf. human parthenotes) or even unregulated (cf. hiPSC) patenting of procedures based on these alleged alternatives becomes increasingly blurred.

[4] The derivation of hpSC from human parthenotes succeeded for the first time in 2007 (Q. Mai et al. Derivation of Human Embryonic Stem Cell Lines from Parthenogenetic Blastocysts. *Cell Res* 2007. DOI: 10.1038/cr.2007.102).

[5] The reprogramming of human somatic cells to hiPSC succeeded for the first time in 2007 (K. Takahashi et al. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* 2007. DOI: 10.1016/j.cell.2007.11.019; J. Yu et al. Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells. *Science* 2007. DOI: 10.1126/science.1151526).

[6] Cf. e.g. C. Simón, A. Pellicer & R. Reijo Pera, ed. 2013. *Stem Cells in Reproductive Medicine. Basic Science and Therapeutic Potential*. 3rd en. Cambridge UP: 85.

[7] ECJ C-34/10, 18 Oct 2011, recital 34.

[8] Ibid: recital 36.

[9] ECJ C-364/13, 18 Dec 2014, recital 29.

[10] Ibid: recital 28.

[11] The term 'human parthenote in itself' refers to a human parthenote that is not the subject of additional manipulation. This procedure will be described in Section 1.

[12] Ibid: recital 17.

Table 1. Patenting of different stem cell types within the EU ([1]hESC: human embryonic stem cells, [2]hpSC: human parthenogenetic stem cells, [3]hiPSC: human induced pluripotent stem cells)

Stem cell type	*Origin*	*Patenting (EU level)*	*Reasoning*	*Normative criterion*
hESC[1]	**Human embryos** (i.e. in vitro fertilized egg cells as well as via SCNT activated egg cells)	**Prohibited** (on the basis of the Biopatent Directive and its interpretations given by the ECJ 2011 and 2014)	Uses of human embryos for commercial and industrial purposes violate their human dignity	**Totipotency**, i.e. inherent capacity of developing into a human being (ECJ 2014)
hpSC[2]	**Human parthenotes** (i.e. via parthenogenesis activated egg cells)	**Permitted** (on the basis of the interpretation of the Biopatent Directive given by the ECJ 2014)	Human parthenotes are not human embryos and therefore do not have human dignity → *First questionable assumption: Human parthenotes are not human embryos*	**No totipotency**: restricted capacity of developing into a human being
hiPSC[3]	**Human somatic cells**	**Not regulated**	Neither human somatic cells nor hiPSC are human embryos and therefore do not have human dignity	**No totipotency**: multipotency (human somatic cells) resp. **pluripotency** (hiPSC) → *Second questionable assumption: HiPSC are not totipotent*

1. TOTIPOTENCY AS A DESCRIPTIVE CRITERION: ARE HUMAN PARTHENOTES REALLY NOT HUMAN EMBRYOS?

Parthenogenesis (Greek '*parthenos*' – virgin, and '*genesis*' – birth) is a form of unisexual reproduction that occurs naturally for example in some kinds of fleas, snails and fishes. Parthenogenesis in humans can be induced artificially by chemically or electrically activating unfertilized egg cells. According to the current state of science it is assumed that human parthenotes are able to develop to the blastocyst stage.[13] Their restricted developmental potential is explained by genomic imprinting, which requires both the maternal and paternal genomes for further embryonic development.[14] In 2004, however, it was shown in the mouse model that the developmental restriction of parthenotes can be overridden by expressing the paternal regulated gene *IGF2* and the maternal regulated gene *H19* within the nucleus of an egg cell.[15] After the implantation of this genetically manipulated nucleus (together with another, unmanipulated nucleus) into an enucleated, unfertilized egg cell, viable parthenogenetic mice were born with the ability to develop to adulthood and to reproduce offspring.

With the criterion 'inherent capacity of developing into a human being' the ECJ excludes human parthenotes from inclusion within the term 'human embryo' (and thus from the attribution of ethical and legal protection). Regarding this criterion, two questions arise[16]:

a. Firstly, to what stage of embryonic development, for example until nidation or birth, do entities have to be able to develop in order to have ascribed to them the 'capacity of developing into a human being'?
b. Secondly, under which necessary external conditions is this capacity still 'inherent' to a cell or an organism?

Regarding question a): The ECJ maintains that human parthenotes are not human embryos due to their restricted developmental potential. As such, in the opinion of the ECJ, a *restricted developmental potential* constitutes an exclusionary criterion for the attribution of the term 'human embryo'. Yet, if entities have to be able to develop to a specific stage of embryonic development, as for example birth, in order to be ascribed with the 'capacity of developing into a human being' and to be referred to as human embryos, most of the entities that we usually term 'human embryos' could not be described as such, because approximately 80% of all embryos, both in vitro and in vivo, do not reach[17] the stage of

[13] Cf. N. T. Rogers et al. Phospholipase Czeta Causes Ca2+ Oscillations and Parthenogenetic Activation of Human Oocytes. *Reproduction* 2004. DOI: 10.1530/rep.1.00484.

[14] M. J. Escriba et al. New Techniques on Embryo Manipulation. *J Reprod Immunol* 2002; 55: 149–161.

[15] T. Kono et al. Birth of Parthenogenetic Mice that Can Develop to Adulthood. *Nature* 2004. DOI:10.1038/nature02402.

[16] Cf. similarly H.-G. Dederer. Anmerkung zum Urteil des EuGH in der Rechtssache C-364/13 vom 18.12.2014. *GRUR* 2015: 156–159. Aside these two aspects of the ruling, the difference from the two decisions of the German FCC on termination of pregnancy is also striking. This aspect will be addressed in section 2.

[17] Strictly speaking, the human embryo can of course never achieve the stage of birth as it is called foetus from the 11th week of pregnancy until birth.

birth.[18] It might be rightly objected that the attribution of the term 'human embryo' is based not on an entity's actual development but rather on its *typical* development. This means that an entity *a* called 'human embryo' falls under a class of entities (extension) that are typically able to develop until birth regardless of the actual development of entity *a*.[19] It is concluded that human parthenotes are not human embryos as they are typically not able to reach the stage of birth. However, in light of the fact that certain (sub)classes of embryos also do not typically reach the stage of birth (for example embryos with chromosome aberrations like monosomies, trisomies etc., that lead to an early abortion) and are nevertheless referred to as human embryos (and protected in the same way), this conclusion regarding the designation of human parthenotes is wrong. Thus, there is no reason why parthenotes should not also form a subclass of human embryos that typically do not reach the stage of birth. Moreover, within developmental biology a restricted developmental potential does not constitute an exclusionary criterion for the attribution of the term 'human embryo'. With regard to mammals (including humans) it is common to call entities in the foetal period *foetuses* and entities in the embryonic phase *embryos*, irrespective of whether they reach birth or not.[20] Therefore, scientific publications refer to human parthenotes – in parallel with aneuploid embryos[21] (embryos with chromosome aberrations) and anencephalic embryos[22] (embryos with anencephaly) – as parthenogenetic embryos[23].

In addition, the mandate for a potential development until birth loses its significance in light of the problem that there aren't and cannot be any scientific findings on the question of how far human parthenotes can in fact develop in vivo, as the transfer into the uterus of a woman is prohibited worldwide. In the absence of such proof, human parthenotes are comparable with human clones that would evolve from SCNT which, in keeping with the prohibition on reproductive cloning, cannot be transferred and brought to birth.[24] In the case of human clones, conclusions are thus drawn from the development of mammalian clones. As was shown in many animal species since the first born mammalian clone 'Dolly' in 1996,[25] they are able to develop to adulthood and to reproduce offspring with, however, an above average propensity to develop diseases and with a shorter life expectancy due to their genomic imprinting.[26] Correspondingly, it has been shown that mammalian parthenotes, too, are able to develop restrictedly in vivo[27] without genetic manipulation and also, after genetic manipulation, until birth, with the ability to develop to adulthood and to produce offspring.[28] Therefore, we have to assume that human parthenotes might be able to develop until birth (at least in conjunction with genetic manipulation).

Regarding question b): The ECJ does, however, distinguish between 'a human parthenote in itself' and 'a parthenote which is the subject of additional manipulation'.[29] According to this line of thinking, a human parthenote is not a human embryo because it would require *additional external conditions* to develop until birth. However, considering the fact that even human embryos created by fertilization (in vitro as well as in vivo), which constitute a point of reference for the ECJ's definition of the term 'human embryo', require numerous external conditions to be able to develop into a human being, the question arises which necessary external conditions still allow for the 'capacity of developing into a human being' to be regarded as inherent. The distinction between the respective developmental potentials of a human parthenote in itself and an additionally genetically manipulated human parthenote is thereby supported by three main arguments: Firstly, the *normality* of the embryonic development. It is argued

[18] Birth rates within in-vitro fertilization (IVF) and in natural reproduction range from 15 to 20% per (treatment) cycle. Chromosomal abnormalities are believed to be a major reason for the occurrence of spontaneous abortion (cf. L. K. Moore. 2015. *Before We Are Born: Essentials of Embryology and Birth Defects*. Philadelphia, PA: Saunders/Elsevier: 27; German IVF register. 2011. World Preliminary Report on ART. Available at: http://www.deutsches-ivf-register.de/perch/resources/downloads/jre32015eshreicmartadamson.pdf [Accessed 15 Sept 2016]).

[19] The distinction between actual and typical development does not refer to an ontological category, but in a logical sense to properties that serve to define sortals. In this sense, a certain entity falling for example into the extension of the sortal 'human being' can have a property either actually (like belonging to the species homo sapiens) or only typically (like the capacity for reason).

[20] S. F. Gilbert. 2013. *Developmental Biology*. Massachusetts: Sinauer Associates Inc.: 25ff.

[21] Cf. e.g. M.C. Magli et al. Chromosome Mosaicism in Day 3 Aneuploid Embryos that Develop to Morphologically Normal Blastocysts In Vitro. *Hum Reprod* 2000. DOI: 10.1093/humrep/15.8.1781.

[22] Cf. e.g. J. E. Frazer. Report on an Anencephalic Embryo. *J Anat* 1921; 56: 12–19.

[23] Cf. e.g. Z. Chen et al. Birth of Parthenote Mice Directly from Parthenogenetic Embryonic Stem Cells. *Stem Cells* 2009. DOI: 10.1002/stem.158.

[24] As expressed, for example, in the Universal Declaration on the Human Genome and Human Rights from 1997, art. 11.

[25] I. Wilmut et al. Viable Offspring Derived from Fetal and Adult Mammalian Cells. *Nature* 1997. DOI: 10.1038/385810a0.

[26] Cf. e.g. D. Humpherys et al. Epigenetic Instability in ES Cells and Cloned Mice. *Science* 2001. DOI: 10.1126/science.1061402.

[27] It has been shown, that dog parthenotes, for example, are able to develop in vivo until day 28 (cf. J. E. Park et al. Altered Cell Cycle Gene Expression and Apoptosis in Post-Implantation Dog Parthenotes. *PLOS One* 2012. DOI: 10.1371/journal.pone.0041256) and pig parthenotes until day 31 (cf. J. Zhu et al. In Vitro and In Vivo Developmental Competence of Ovulated and In Vitro Matured Porcine Oocytes Activated by Electrical Activation. *Cloning and Stem Cells* 2003. DOI: 10.1089/153623003772032853).

[28] Kono et al., *op. cit*. note 15.

[29] ECJ C-34/10, 18 Oct 2011, recital 35.

that if the development of a human embryo created by fertilization proceeds normally, it develops into a human being. But if the development of a human parthenote proceeds normally, that is to say without additional manipulations, it does not develop into a human being.[30] The reference to a normal development might make sense in the context of human embryos in vivo, but what does a normal development mean with regards to either human embryos in vitro or human parthenotes? This seems to depend on the way in which they are defined. Embryos in vitro are de facto produced for research purposes as well as for reproduction purposes: for embryos in the context of reproduction, a normal development means to be implanted into a woman's uterus. For research-embryos a normal development means to be destroyed in the blastocyst stage. Correspondingly, since we want to produce human parthenotes for research purposes, a normal development for a parthenote would mean to be destroyed in the blastocyst stage. But if we wanted to produce human parthenotes for reproduction purposes, a normal development for a parthenote would mean to be implanted into a woman's uterus. Obviously we do not want the latter, but if we did, we would provide all enabling conditions that are necessary for the parthenote to be able to achieve its full potential, which would include the genetic manipulation of one of the egg cells involved in its formation.[31] Therefore, the argument that human parthenotes are not human embryos because they are not able to develop 'normally' into human beings, whereby a normal development of a parthenote is defined as not developing into a human being, is a circular argument.

Secondly, the distinction between *naturalness and artificiality*. It is argued that human parthenotes are not human embryos but only hominid 'quasi-embryos' not worthy of protection as their potential to develop into human beings would depend on artificial induction.[32] However, the criterion of naturalness goes decidedly too far as it excludes not only human parthenotes (both with and without genetic manipulation) but also human clones and even human embryos in vitro which are almost undisputedly referred to as human embryos (and are protected accordingly).

Thirdly, instead of referring to a qualitative distinction (normal, natural) between the respective developmental potentials of a human parthenote in itself and an additionally genetically manipulated human parthenote, a classificatory distinction is made between those two types of human parthenotes by suggesting that genetically manipulated parthenotes are not human parthenotes at all. According to the German Research Foundation (DFG), for example, the designation of the animals referred to in the publication by Kono et al. as 'parthenogenetic mice' was incorrect because 'parthenogenetically generated [mammalian including] human blastocysts in fact cannot develop into living organisms'.[33] However, this reasoning, too, is circular. The assumption that mammalian parthenotes cannot develop into living organisms is an assumption that basically can be and clearly has been disproved by the experiment of Kono et al. It is therefore not a sound basis for the attribution of the term 'parthenote' (whether mammalian or human) to certain entities. Similarly, Beck argues that genetically manipulated and activated egg cells are '*false parthenotes*' that in fact emerged from fertilization with a manipulated set of female chromosomes instead of sperm.[34] However, this argumentation ignores the fact that both entities ('real' and 'false' parthenotes) are two different types of parthenotes that emerged from two different parthenogenetic procedures and are in both cases derived from only egg cells.[35] Thus, the supposition that human parthenotes do not have the potential to develop into human beings is based on the reinterpretation of human parthenotes that do have this potential as 'false parthenotes'.

This examination shows that human parthenotes are not delimitable from human embryos that emerge from fertilization on the basis of the ECJ's narrow 2014 definition of the term 'human embryo'. Human parthenotes cannot be consistently denied an 'inherent capacity of developing into a human being', either by the determination of an endpoint in embryonic development that ought to be achieved, like birth, or by the exclusion of

[30] Cf. Advena-Regnery et al. Sind Parthenoten Embryonen? *ZfmE* 2015; 61: 151–167: 166f.

[31] From the consensus on the banning of reproductive cloning it can be concluded that there is also a consensus to not implant and bear human parthenotes, at least since it would involve too much risk concerning the health of the child that would emerge from this procedure.

[32] Cf. e.g. Advena-Regnery et al., *op. cit*. note 30, pp. 161f.; H. Kress. 2009. *Medizinische Ethik. Gesundheitsschutz – Selbstbestimmungsrechte – heutige Wertkonflikte*. Stuttgart: Kohlhammer: 180. The French philosopher Bruno Latour contributed a lot to the scrutinization and critical mapping of so-called quasi-objects (Cf. B. Latour. 2014. How Better to Register the Agency of Things. Available at: http://www.bruno-latour.fr/sites/default/files/137-YALE-TANNER.pdf [Accessed 15 Sept 2016]; B. Latour. 1993. *We Have Never Been Modern*. Massachusetts: Harvard UP).

[33] Deutsche Forschungsgemeinschaft (DFG). 2006. *Stammzellforschung in Deutschland – Möglichkeiten und Perspektiven. Stellungnahme*. Bonn: DFG. Available at: http://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/2006/stammzellforschung_deutschland_lang_0610.pdf [Accessed 15 Sept 2016]: 131.

[34] Cf. M. Beck. 2009. *Mensch-Tier-Wesen. Zur ethischen Problematik von Hybriden, Chimären, Parthenoten*. Paderborn: Schöningh: 95ff.

[35] This is also confirmed by the scientific publications in the field of research on parthenogenesis (e.g. Kono et al., *op. cit*. note 15; R. B. Northrop & A. N. Connor. 2009. *Introduction to Molecular Biology, Genomics and Proteomics for Biomedical Engineers*. Boca Raton, FL: CRC Press: 359; P. W. Lampton, J. A. Newmark & A. A. Kiessling. 2013. Generation of Histocompatible Tissues via Parthenogenesis. In *The Immunological Barriers to Regenerative Medicine*. P. J. Fairchild, ed. New York: Humana Press: 129–146: 132).

required additional external conditions. These criteria are not even met by human embryos which emerge from fertilization, as they, too, do not either actually or typically reach birth and need additional external conditions for their development.

Furthermore, the refining attempt to exclude external conditions on the basis that they are not normal or not natural, as well as the suggestion that genetically manipulated parthenotes are not human parthenotes at all, cannot consistently justify a delimitation between entities that are and entities that are not human embryos. According to developmental biology as well as to ordinary language, the attribution of the term 'human embryo' to an entity is independent of its origin (fertilization, SCNT or parthenogenesis), the endpoint of its development (birth) or whether it requires additional external conditions to reach that endpoint. Consequently, totipotency as the capacity (or in the wording of the ECJ, even inherent capacity) to develop into a (born) human being is *not a necessary condition* for the attribution of the term 'human embryo'. The fact that a human entity has at least some developmental potential is sufficient for calling it a human embryo.[36] However, the conclusion that human parthenotes are also human embryos is at this point a purely descriptive statement that must be separated from the question of whether human parthenotes are worthy of protection, since the attribution of the term 'human embryo' and the attribution of a protection status may depend on different criteria. Within the ethical and legal debates on the handling of human parthenotes, the descriptive question of whether human parthenotes fall into the extension of the term 'human embryo' and the normative question of whether human parthenotes should be protected in the same way as human embryos are often imprecisely treated as one question: whether parthenotes are human embryos or not. This question is then examined from a normative starting point: 'Should human parthenotes be protected in the same way as human embryos?' And the answer to that (i.e. 'Probably not.') is transferred to a normatively loaded yet actually descriptive conclusion: 'Human parthenotes are not (meaning: can, should or even must not be) human embryos'. This leads to *counterintuitive* outcomes, such as calling human parthenotes 'quasi-embryos', which basically suggests that human parthenotes are indeed human embryos (in a descriptive sense), but that, at the same time, they should not be protected in the same way. Based on the argumentation above, it also leads to *false* conclusions, such as the statement that from a normative viewpoint, the term 'human embryo' is obviously inappropriate to denote human parthenotes.[37] The attribution of a term to a certain entity is purely descriptive and does not depend on normativity.

After examining the attribution of the term 'human embryo' to human parthenotes based on totipotency as a *descriptive* criterion, the next section will examine the attribution of totipotency as a *normative* protection criterion to certain entities thus worthy of protection and the delimitation to other entities that are not worthy of protection on that basis with the example of tetraploid complementation assay using iPSC and pSC (see table 1, second questionable assumption).

2. TOTIPOTENCY AS A NORMATIVE PROTECTION CRITERION: ARE HIPSC REALLY NOT TOTIPOTENT?[38]

Within the classical debate on the moral status of human embryos, reference is made to totipotency as a normative protection criterion by means of the potentiality argument (PA). According to this, already human embryos fall under the purview of dignity and the protection of life as they potentially possess those intrinsic properties that are decisive for the attribution of such a protection status, due to their capacity to develop into born human beings. By these means, PA classically aims at justifying an equally strong protection status for human embryos as for born humans. However, PA is increasingly coming under pressure in light of the technological advances in the field of stem cell research. With regard to human parthenotes, for example, it is inconsistent for PA not to protect them in the same way as it protects human embryos. Firstly, PA also protects human embryos that actually (as in 80% of all embryos in vitro and in vivo) or also typically (such as embryos with chromosome aberrations) do not develop until birth. Secondly, in light of the fact that there are not and cannot be any scientific findings on the question of how far human parthenotes can in fact develop in vivo, it cannot be ruled out that they could develop further than the blastocyst stage.[39] Thirdly, in the absence of such proof, analogies from the animal model do show that parthenotes are actually able to develop until birth after genetic manipulation. As such, it can be assumed that the ECJ itself based its assumption that human embryos have human dignity on PA. In contrast to the two decisions of the German

[36] Cf. similarly J. S. Ach, B. Schöne-Seifert & L. Siep. 2006. Totipotenz und Potentialität. In *Jahrbuch für Wissenschaft und Ethik 11*. L. Honnefelder & D. Sturma, ed. Berlin, Boston: De Gruyter: 261–321: 308.

[37] 'Thereby, the term 'human embryo' may be suitable for the human parthenote in a biological sense, from a normative viewpoint it is obviously inappropriate.' (Advena-Regnery et al., *op. cit*. note 30, p. 162).

[38] See also H. Schickl et al. Abweg Totipotenz. Rechtsethische und rechtspolitische Herausforderungen im Umgang mit induzierten pluripotenten Stammzellen. *MedR* 2014. DOI: 10.1007/s00350-014-3863-4.

[39] Cf. similarly Ach et al., *op. cit*. note 38, p. 311.

Federal Constitutional Court (FCC) on the termination of pregnancy, the ECJ states that human embryos develop 'into' human beings and not 'as' human beings, which means that human embryos in general are not yet, but are still becoming human beings.[40] Therefore, their assumed dignity cannot be founded in their being human, but only in their capacity to become human beings. With regard to tetraploid complementation assay using iPSC, the criticism of PA goes even further than merely a reproach of inconsistency.

The ethical and legal questions arising with respect to hpSC and hiPSC as alternatives to hESC refer to the same criterion (totipotency), but arise at different levels. On the one hand, at the level of the stem cell type and, on the other hand, at the level of the origin of the stem cell type (see Table 1): The currently discussed normative question regarding the use of human parthenotes as an alternative source to hESC is whether or not human parthenotes should be protected in the same way as human embryos. Regarding the use of hiPSC as an alternative to hESC derived from human embryos, the decisive normative question is whether these stem cells are actually pluripotent. Initially, there was doubt about whether hiPSC reprogrammed from unipotent human somatic cells are actually pluripotent or still unipotent. These doubts were dispelled in 2009 when a generation of viable mice from iPSC by tetraploid complementation assay was assumed to prove the pluripotency of iPSC.[41] In this procedure, diploid cells of a (mouse) embryo are merged to cells with a double set of chromosomes. After complementing this tetraploid cell complex with iPSC, a blastocyst develops which develops in vivo into a viable mouse. Thereby, the restrictedly developable tetraploid cell complex solely forms the trophoblast. However, in view of the fact that in the course of this process an obviously totipotent blastocyst emerges from considered pluripotent iPSC, the clarity of the attribution of pluripotency to hiPSC becomes blurred. Since the transferability of this procedure to humans is basically possible, the question arises of whether the *inherent capacity* to develop into a born human must also be assigned to hiPSC and to human somatic cells. For the sake of consistency, if hiPSC as well as human somatic cells have developmental potential, PA ought to already place every human somatic cell under the protection of life and dignity (*absurd extension argument*).[42] Moreover, as tetraploid complementation assay also succeeded using mammalian pSC in 2009, the same conclusion is valid for hpSC and human parthenotes.[43] Curiously, the ethical debate on human parthenotes has a strong focus on their developmental potential while neglecting the developmental potential of hpSC.

To avoid the absurd outcome of having to place every human somatic cell under the protection of life and dignity, proponents of PA provide further criteria that restrict the developmental potential in order to normatively delimit the developmental potential of a human embryo from that of other human cells. These criteria are then related to the exclusionary criterion of *additional external conditions* and refer to the *naturalness* (vs. artificiality) and the *activity* (vs. passivity) of the potential. Within this context, the naturalness argument emphasizes that human embryos develop naturally into a human being whereas this development would need to be induced artificially with regard to hiPSC and human somatic cells.[44] However, as already mentioned in Section 1, the criterion of naturalness goes too far as it excludes not only hiPSC and human somatic cells from protection but also human embryos in vitro, which also have to be artificially transferred into a uterus. This, however, undermines the general thrust of PA which aims at protecting embryos in vitro against their destruction in the course of embryo research. With the distinction between active and passive, the potential of the human embryos is specified as an active one, i.e. the potential to develop 'from within' without further interventions (except necessary environmental conditions) into a born human being. It is assumed that the entire active potential of the future born human being is already present within the zygote and only requires the opportunity to develop gradually. In contrast, the potential of hiPSC and human somatic cells is considered as a merely passive one that would require an additional act in order to become real.[45] But in fact, all the genetic information that is necessary for the reprogramming and further development of human somatic cells is also already present within every human somatic cell. To be sure, a human somatic cell's potential

[40] Cf. German FCC 39, 1, 25 February 1975, recital 37; similarly, 88, 203, 28 May 1993, recital 252.

[41] X. Zhao et al. iPS Cells Produce Viable Mice through Tetraploid Complementation. *Nature* 2009. DOI: 10.1038/nature08267; L. Kang et al. iPS Cells Can Support Full-Term Development of Tetraploid Blastocyst-Complemented Embryos. *Cell Stem Cell* 2009. DOI: 10.1016/j.stem.2009.07.001.

[42] Cf. similarly M. Stier & B. Schöne-Seifert. The Argument from Potentiality in the Embryo Protection Debate: Finally 'Depotentialized'? *Am J Bioeth*. 2013; 13: 19–27. DOI: 10.1080/15265161.2012.743619; M. Stier. Tetraploide Komplementierung von iPS-Zellen: Implikationen für das Potenzialitätsargument. *Ethik Med* 2014; 26: 181–194. DOI 10.1007/s00481-013-0254-8.

[43] Chen et al., *op. cit*. note 23.

[44] Cf. e.g. B. Advena-Regnery et al. Totipotenz im Spannungsfeld von Biologie, Ethik und Recht. *ZfmE* 2012; 3: 217–236: 229f.; J. Reich. Empirische Totipotenz und metaphysische Gattungszugehörigkeit bei der moralischen Beurteilung des vorgeburtlichen menschlichen Lebens. *ZfmE* 2004; 50: 115–130: 125ff.

[45] Cf. e.g. Beck et al., *op. cit*. note 36, p. 34f.; M. Quante. 2002. *Personales Leben und menschlicher Tod. Personale Identität als Prinzip der biomedizinischen Ethik*. Berlin: Suhrkamp: 101ff.

to develop into a human being would require an additional act, but it is not clear why the transfer of human embryos in vitro into a uterus should be considered as 'merely' providing the *necessary environmental condition* while the reprogramming of human somatic cells and the complementation of hiPSC in contrast count as an *additional act*.

To sum up, the technological advances in generating viable organisms from iPSC and pSC using tetraploid complementation assay and the possible transfer of this procedure to humans leads to the conclusion that human embryos are not normatively delimitable from other human cells like hpSC, human parthenotes, hiPSC and human somatic cells on the basis of PA and the ECJ's 2014 criterion for the designation of human embryos and a concomitant protection status. Human somatic cells cannot be consistently denied the potential, or the 'inherent capacity', to develop into a (born) human being by claiming that their developmental potential must be natural or active to be worthy of protection, as this does not also apply to the developmental potential of human embryos in vitro, which are considered as worthy of protection according to both PA as well as the ECJ. Subsequently, totipotency (or developmental potential) is *not a sufficient condition* for the attribution of a normative protection status to certain entities.

CONCLUDING REMARKS

This analysis has shown that human embryos worthy of protection are not consistently delimitable from human parthenotes (or even from hpSC, hiPSC and human somatic cells) not worthy of protection on the basis of the ECJ's criterion 'inherent capacity to develop into a human being' (or totipotency). Consequently, the strict delineation between an ethically problematic commercial use of human embryos and the concomitant patenting prohibition of hESC-based procedures and an ethically unproblematic commercial use of human non-embryos and the therefore either unrestrictedly permitted (cf. human parthenotes) or even unregulated (cf. hiPSC) patenting of procedures based on these alleged alternatives is not sustainable.

The general patenting exclusion of procedures that are associated with the commercial use of human embryos lacks a legal differentiation between a descriptive attribution of the term 'human embryo' and a normative attribution of a protection status to certain entities. This lacking differentiation leads to false and counterintuitive (cf. particularly human parthenotes) or absurd (cf. particularly hiPSC) consequences within the current legal practice and ethical debate on the patenting prohibition. Decoupling these two different levels from each other would allow for a purely descriptive designation of human parthenotes as human embryos without thereby automatically ascribing to them a normative protection status. Such a basis would additionally allow for a more honest deliberation, in a second step on a normative level, as to which human embryos should be protected from commercial exploitation and for what reasons, without thereby automatically basing their normative protection on their totipotency or developmental potential. This deliberation requires a democratic process within society on the questions of which kind of human embryos or cells can or should be used (what?) based on which normative criteria (why?) and for what purposes (wherefore?); questions that will ultimately also have consequences for the problem of which kind of cells could and should be subject to commercial exploitation or part of patenting. The normative protection status of human embryos can thereby, for example, not only be based on intrinsic criteria (like developmental potential), but also on extrinsic criteria like the purpose and context in which these entities are produced and used (such as research, reproductive or clinical contexts). It can also be based on considerations regarding people's feelings of piety surrounding human embryos in analogy to human corpses or organs. Both suggested positions would imply a lower (in relation to the first) or even much lower (in relation to the second) protection status than PA classically intends and would also lead to the conclusion that there may be human embryos that are not worthy of protection; a conclusion that is considered extremely dangerous for proponents of PA and the so-called 'protectors of life' who emphasize the importance of drawing a clear line between human beings worthy of protection and other organisms that are not (or at least not equally) worthy of protection. However, as it has been shown in this article, this alleged clear delimitation between human embryos worthy of protection and human non-embryos not worthy of protection can no longer be consistently sustained.

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