Invention and the Human Embryo

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Should the 14-day rule for research on human embryos be applied to biotechnology inventions?

Introduction

Uses of human embryos for commercial or industrial purposes are excluded from patentability because this would be contrary to *ordre* public or morality. Nevertheless, advances at the frontiers of stem cell science and its clinical translation require significant investment. If it is accepted that the patent system, an anti-competitive *force majeure* is tolerable for society because of its unrivalled incentive *to invest*[1] in high-risk research, it follows that absence of this incentive is likely to exert a chilling effect on commercial investment, that in turn may compromise the social mission of stem cell research to meet hitherto unmet medical and public health needs.

The prohibition has been interpreted by the Enlarged Board of Appeal and the CJEU. The European Group on Ethics, which had previously expressed the opinion that patenting inventions using human stem cells from embryonic

[1] See generally, M Fisher, Fundamentals of Patent Law: Interpretation and Scope of Protection (Hart, 2007).

origin to create genetically modified stem cell lines, or specific differentiated stem cell lines for specific therapeutic or other uses was ethically acceptable,[2] was inexplicably overlooked. Both judgments declared the embryo as "fully human" from being a single-cell (zygote) owing to its newly created genome, the zygote being the first stage of a human being. Avoiding examination of the ethical debate on embryos as persons, it was held that the embryo's dignity demanded protection from harm caused by being used in a commercial context.

In arriving at this interpretation of 'human embryo', two assumptions were made. First that a reasonably clear conception of human dignity exists to provide a substantive interpretation in the patent context, which I suggest it doesn't.[3] Second, that each embryo lawfully donated for use in research or therapy in accordance with consent procedures (e.g. required by the HFEA in the UK) would otherwise be implanted into a willing uterus. Without this certainty, there can be no new person.

The prohibition against "use" of human embryos on the basis of its moral status in *patent law* sits uncomfortably with what is widely considered ethical use (including destruction) *outside of it*. For example, the approach to human embryo "use" in research and development is tangential to that adopted in patent jurisprudence. Yet this "use" accords with widely shared ethical

[2] EGE Opinion no. 16, Ethical aspects of patenting inventions involving human stem cells, 7 May 2002, para 2.4.
[3] See C McCruddon, Human Dignity and Judicial Interpretation of Human Rights' EJIL (2008) 19 (4), 655 - 724.

principles in science and medicine.[4] Known as the "14-day rule" it was recommended in the Warnock Report in 1984 and has since formed part of the regulations of the UK's Human Fertilisation and Embryology Act 1990 (as amended) until the present date.

Another example of ethically acceptable embryo "use" is for fertility treatment e.g. IVF, which is only available on the NHS if certain criteria are met.[5] If not, those with a child-wish must go private. Before choosing whom to go with people generally research providers on-line and visit fertility shows[6] to compare success rates, payment options[7] and so on. This has led to increased branding and marketing; the fertility sector is apparently 'big business'.[8] In the UK all assisted reproductive treatment (ART) involving *in vitro* human embryo creation, and research involving human embryos and their manipulation is regulated by the Human Fertilisation and Embryology Authority (HFEA) under the provisions of the Human Fertilisation and Embryology Acts 1990 and 2008. The 2008 Act amends the law relating to assisted reproduction and embryo research to reflect scientific developments and changes in social attitudes. It applies to all live human embryos

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[4] Nuremberg Code, 1949; Department of Health, and Education and Welfare, 1979; European Science Foundation, 2000; Medical Professionalism Project, 2002; Institute of Medicine, 2009; World Medical Association, 2013.

[5] https://www.nhs.uk/conditions/ivf/availability/. For example, couples at >10% risk of having a child with a serious genetic condition may obtain three cycles of IVF/ICSI in conjunction with pre-implantation genetic diagnosis: NHS Commissioning Board, 'Clinical Commissioning Policy: PGD' (April 2013), ref. NHSCB/E 01/P/a.

[6] The Fertility Show in London attracts over 1.6 million https://olympia.london/whatson/fertility-show

[7] 'Care' the largest provider of fertility services in the UK offers IVF refund and pre-pay plans with 'up to 100% refund if you don't have a baby': https://www.carefertility.com/costs/ivf-refund-and-pre-pay-plans/

[8] M Frith, 'You're big business now, baby' *The Telegraph* (19 Oct 2014), quoting K Grassby (Bowmark Capital Private Equity Group).

regardless of the manner of their creation, in the UK. The list of purposes for which research may be licensed (Human Fertilisation and Embryology (Research Purposes) Regulations (SI 2001/188)) has been expanded in new paragraph 3A(2)(a) to include research to increase knowledge, not only about serious diseases, but also about other serious medical conditions such as neural trauma or other tissue damage, which would not be considered to be diseases and therefore would not previously have been permitted.

However the mainstay of the expanding fertility industry is predicated on commercial "use" of human embryos for the provision of fertility services pursuant to contractual arrangements.[9] An unprofitable IVF clinic will soon cease to trade.[10] It is also to the point that an objective of fertility treatment is not to transfer each and every embryo created. Only the best may be transferred, providing a commercial incentive for clinics to maximize success rates e.g. by creating a higher number of embryos to choose from. Many embryos may be created over the course of treatment but only one or two selected for uterine transfer per cycle. Preimplantation diagnostic testing (PGD) may reduce this number further. The fate of surplus and left-over IVF embryos depends on the client(s) wishes. The ECtHR has ruled that ability to exercise a conscious and considered choice regarding the fate of ones embryos concerns an 'intimate aspect of personal life' that relates to the right to self-determination, protected under article 8 of the Convention.[11] The client(s) may lawfully choose to allow the embryos to thaw and perish, or to pay to keep

[9] The average cost of one IVF treatment using client's own eggs is £3455-£4995, or with a fresh donor egg, £7875. Figures obtained from www.ivi.uk and www.manchesterfertility.com (accessed May 2019).
[10] See M Frith, 'You're big business now, baby' *The Telegraph* (19 Oct 2014) reporting that the expanding UK fertility industry is worth over a £1billion.
[11] *Parrillo v Italy* [2015] ECHR, [159].

some frozen for use in the future. Alternatively the client(s) may donate their embryos for other uses, for example to someone in need, or for use in research, or to donate them for embryologists to practice on (e.g. removing cells, or freezing/thawing techniques).

The question I pose is whether the 14-day rule for research on pre-implantation human embryos ought to extend to the sphere of patent law to permit the patentability of a wider range of innovation in embryonic stem cell science to benefit society? Or does the principle of human dignity preclude such a bold suggestion?

The paper is structured as follows. Part 1 traces the development at the CJEU and EPO of morality jurisprudence relevant to human embryos. Other contexts that "use" the human embryo are explored.[12] Conflicting notions of the embryo's *status* represented in the HFEA regulatory framework and in patent jurisprudence are identified. The section moves on to explore whether the exclusion from patentability of subject matter that commercially uses human embryos is meeting legislative objectives by conducting searches for published patents in order to obtain a snapshot of current activities in the field. Part 2 explores whether a reasonably clear conception of human dignity exists to provide a basis for substantive interpretation of patent law. The conclusion follows.

Defining terms

[12] T 866/01 *Euthanasia Compositions*. MICHIGAN STATE UNIVERSITY (2005) at 6.12 of the Reasons.

The paper will be more clearly understood if certain terms used throughout are defined, although defining the entity "human embryo" is not a straightforward matter. Classical embryology uses the term "embryo" to connote different post-implantation stages of development such as emergence of the primitive streak.[13] Others consider the embryo as such once attached to the uterine wall (nidation).[14] "Fertilization" refers to the penetration of the human ovum by spermatozoon, the combination of their genetic material resulting in the formation of a zygote. "Embryo" is the product of the division of the zygote to the end of the embryonic stage at around eight[15] or nine[16] weeks after fertilization. The cleavage stage of the embryo occurs during the first three days of culture. After about five days, the embryo reaches the blastocyst stage, defined by pumping of fluid into the blastocoel cavity, the stage in issue in the *Brustle* case, discussed below. The blastocyst's outer layer is a ring of trophectoderm cells, which is the precursor to the placenta. The trophectoderm ring encloses a nest of 10-25 cells called the "inner cell mass" from which embryonic stem cells (ES cells) can be derived. Human ES cells are derived from an embryo. Stem cells are classified by their development potential as: (1) totipotent, meaning capable of giving rise to all types of differentiated cells found in an organism, as well as the supporting extra-embryonic structures of the placenta. A single totipotent cell could, by

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[13] International Society for Stem Cell Research (ISSCR), '*Guidelines for stem cell research and clinical translation*', May 2016, 32.

[14] Dorland's Illustrated Medical Dictionary (27th edition, 1988 edition, W.B. Saunders Company); Random House Webster's College Dictionary, both cited in International Society for Stem Cell Research (ISSCR), '*Guidelines for stem cell research and clinical translation*', May 2016, 32.

[15] The moral status of the pre-implantation embryo: ESHRE Task Force on Ethics and Law, *Human Reproduction*, Volume 16, Issue 5, 1 May 2001, Pages 1046–1048, https://doi.org/10.1093/humrep/16.5.1046

[16] International Society for Stem Cell Research (ISSCR), '*Guidelines for stem cell research and clinical translation*', May 2016, available at www.isscr.org.

division in utero, reproduce the whole organism; (2) pluripotent, meaning able to give rise to all embryonic cell types; (3) multipotent, meaning able to give rise to a subset of cell lineages but all within a particular tissue, organ or physiological system (4) oligopotent, meaning able to give rise to a more restricted subset of cell lineages than multipotent stem cells; and unipotent, meaning able to give rise to a single cell lineage (e.g. spermatogenic stem cells).

They are a specific class of stem cell that are pluripotent, that is they have the capacity to develop into *every type* of cell needed for full fetal development - but not the placenta or umbilical cord. A pluripotent stem cell cannot develop into a human being because it cannot form the necessary infrastructure to sustain a pregnancy. Pluripotent stem cells are distinguished from stem cells derived from older embryonic or fetal tissue, which have far less ability to differentiate into different cell types according to the scientists needs.[17] Embryonic stem cells appropriate for use in clinical research and application[18] can be processed and maintained in a line and increased in number for prolonged periods in appropriate culture conditions.[19] Differentiation is the process by which an unspecialized or less specialized cell acquires the features of a specialized cell such as, for example, a nerve cell or muscle cell.

To do hESC research and develop new treatments requires a plentiful source of hESCs, which there are not. These type of cell remain highly desirable.

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[17] MRC Code of Practice for the use of human stem cell lines, Version 5 (2010).
[18] Regulated by the EU Directive on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Storage and Distribution of Human Tissues and Cells, transposed into the UK as the Human Tissue (Quality and Safety for Human Application) Regulation 2007.
[19] MRC Code of Practice for the use of human stem cell lines, Version 5 (2010).

Although the study of induced pluripotent stem cells[20] (iPS cells) excites the possibility of a different source of these cells[21], considerable work remains to be done to ensure these can be isolated and used safely and routinely.[22] Once established, ES cell lines are not a line of human embryos (being pluripotent) and are not subject to the same level of regulation as embryo research.[23]

Patent law however, does not make this distinction. New and specialized pluripotent stem cells for use in treatment cannot be patented where the creation of the cell line from which it derives has involved a sacrificed human embryo at some (even distant) point before. This fact alone precludes the patentability of all derivatives of that embryo according to a doctrine of complicity established in WARF and *Brustle*, to which we now turn.

The Law

The protracted passage of Directive 98/44/EC on the legal protection of biotechnology ("the Directive") and its coming into force was notable if for no other reason than the sense of outrage it provoked in people who believed it transgressed an acceptable line in patent law between discovery and invention, serving to monopolise "life" itself. Shortly after coming into force, a full frontal attack spearheaded by the Kingdom of the Netherlands

[20] A reprogrammed adult cell that behaves like an embryonic stem cell (i.e. pluripotent).
[21] With the benefit of tissue compatibility with the patient.
[22] ISSCR 'Stem Cell Facts'. Interestingly, a patent has been filed at the EPO that claims a method of producing hESCs without destroying the human embryo, leaving it viable: AU2018220130 (13/9/2018).
[23] MRC Code of Practice for the use of human stem cell lines, Version 5 (2010) p. 2

followed, an appeal for annulment that was rejected,[24] after which the Commission had cause to refer eight Member States to the European Court of Justice (CJEU) for their failure to implement the Directive.[25] Despite these earlier difficulties, the Directive was eventually implemented into national laws across the European Union.[26]

There is no doubt that promoting investment in the biotechnology was (and remains) an important objective of the EU legislature.[27] Nevertheless, patent law must be applied to respect morality and *ordre* public:

'Whereas ordre public and morality correspond in particular to ethical or moral principles recognized in a member state, respect for which is particularly important in the field of biotechnology in view of the potential scope of inventions in this field and their inherent relationship to living matter; whereas such ethical and moral principles supplement the standard legal examinations under patent law regardless of the technical field of the invention.'[28]

Furthermore, patent law must be applied to respect fundamental principles recognized in EU law safeguarding the dignity and integrity of the person,[29]

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[24] C-377/98 Netherlands v Parliament and Council [2001] ECR I-7079.
[25] ECR [2005], ECJ case 456/03 - *Commission v. Italy*, I-5335.
[26] The UK Patent Regulations came into force on 28 July, 2000: *The Patent Regulations* S.I. No. 2037. Articles 13 and 14 were implemented by the UK on 6 July 2001; Article 12 on 1 March 2002.
[27] In recitals 2,3,4,6,7.
[28] Recital 39.
[29] Recital 16. The Union respects fundamental rights guaranteed by the ECHR pursuant to Art F(2) of the Treaty on European Union embodied in the *constitutional* traditions common to the Member States as general principles of Community law: rec. 43.

'… *whereas it is important to assert the principle that the human body, at any stage in its formation and development, including germ cells and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene cannot be patented; whereas these principles are in line with the criteria of patentability proper to patent law, whereby a mere discovery cannot be patented*.'

Brustle

At the time that *Brustle* was making its way through the courts, legislation and judicial practice within EU Member States, notwithstanding implementation of the Directive, differed according to their understanding of the term "human embryo".[30]

The invention in *Brustle*[31] concerned claims to isolated and purified precursor neural (brain) stem cells obtained from a day-5 embryo including processes for their production. The patent specification described the transplantation of these stem cells into the body's nervous system to allow the treatment of numerous neurological diseases, such as Parkinson's disease.

In issue was whether the invention fell within art 6 (2) (c), which depended on the meaning to be ascribed to 'human embryo', specifically what biological stage in the development of human life this term included. Another important issue concerned claim construction, i.e. whether the invention might

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[30] Opinion on case C- 34/10 (*Oliver Brustle v Greenpeace eV*) (delivered 10 March 2011), [66].
[31] Case C- 34/10 (*Oliver Brustle v Greenpeace eV*) (CJEU 21 Jan 2010).

nevertheless be patentable if the technical teaching claimed does not refer to the 'use' of human embryos.

Delivering his opinion on the case, Advocate General Bot identified two prevalent schools of thought within EU member states, one that viewed the human embryo as coming into existence upon fertilization, the other upon transplantation into the uterus (nidation).[32] In his view, the former was to be preferred because a totipotent cell (the fertilized ova) is the first stage of human development and therefore must be classed as "human embryo". Pluripotent stem cells, lacking inherent capacity to develop into a human being are patentable if obtained without destroying or modifying the embryo from which the cells are sourced.

For the Advocate General, it is the zygote's own genome that confers the status 'human embryo' meaning 'capacity to develop into a human being'. By focusing on the genetic aspect, insufficient attention is given to the necessity of uterine implantation (nidation). This is not to suggest that nidation is sufficient for the embryo to develop into a new human being, but it is *necessary*.

At the CJEU it was observed that the legislative drafting history cast no light on the intended substantive meaning and that the Directive fails to define 'human embryo' or even make reference to national laws in this respect.[33] Acknowledging the 'multiple traditions and value systems' on 'a very

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[32] Opinion on case C- 34/10 (*Oliver Brustle v Greenpeace eV*) (delivered 10 March 2011), [67].
[33] [26].

sensitive social issue',[34] the Court ruled that 'human embryo' must nevertheless designate 'an autonomous concept of European Union law, to be interpreted in a uniform manner throughout the territory of the Union'[35] in accordance with human dignity.[36]

In earlier cases concerning the attack on the Directive and its non-implementation by certain member states, the ECJ (as was) stated the morality and *ordre* public provisions in art 6 (1) of the Directive provided the administrative authorities and courts a wide scope for manoevre, '*to accommodate the social and cultural contexts in which the use of certain patents may give rise to difficulties*'.[37] In contrast art 6 (2)[38] gave none because '*its very purpose is to give definition to the exclusion laid down in Article 6(1)*'.[39] Article 6 (2) provides a non-exhaustive list of subject matter considered to offend *ordre* public or morality (a) processes for human cloning, (b) processes for modification of human germ line identity, (c) use of human embryos for commercial and industrial purposes, and (d) processes for the genetic modification of an animal likely to cause suffering without any substantial benefit to man.

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[34] [30]
[35] [26]
[36] [34].
[37] ECR [2000], case 377/98 - *Netherlands v. Parliament and Council*, I-6229, points 37-39.
[38] A non-exhaustive list of excluded matter includes: processes for human cloning, modification of human germ line identity, use of human embryos for commercial and industrial purposes, and processes for the genetic modification of an animal likely to cause suffering without any substantial benefit to man.
[39] ECR [2005], ECJ case 456/03 - *Commission v. Italy*, I-5335, points 78 and 79.

The problem is, the wording of art 6 (2)(c) leaves open the question *when human life begins*, an issue that even the ECHR Grand Chamber seemed relieved not to have to grapple with recently.[40] To insist on a rigid approach, with no scope for manoevre, is unreasonable in light of the human embryo's disputed status.

As for substantive content,[41] 'human embryo' meant any human ovum after fertilization, since fertilization commences the process of development of a human being.[42] Patentability is excluded when implementation of an invention requires prior destruction of a human embryo, or its use as base material, whatever stage at which that takes place[43] and without explicit reference in the patent as claimed.

Inventions of therapy or diagnosis applied to the human embryo and which are useful to it

The CJEU observed that recital 42 of the Directive provides that inventions of therapy or diagnosis applied to the human embryo and which are useful to it fall outside of the 6 (2) (c) exclusion.[44] So while there can be no patent protection for research activities that use human embryos, a method of diagnosis or therapy *useful* to the human embryo is otherwise patentable subject matter. The type of invention envisaged AG Bot was an operation carried out in utero on an embryo to correct a malformation and to improve

[40] *Parrillo v Italy* [2015] ECHR at [214].
[41] Within the meaning of art 6(2)(c) 98/44/EC.
[42] [35].
[43] [49].
[44] [46].

chances of survival.[45] As I have argued elsewhere,[46] the difficulty in permitting the patentability of diagnostic methods applied to the human embryo is that by definition, such methods serve to *discriminate between embryos* to allow the practitioner to select the 'best' quality, or genetically unaffected embryo. Depending on the PGD test result, the rest are deprioritized for uterine transfer[47] or destroyed.

A new diagnostic method applied to an embryo is only really useful to that embryo *if* the diagnostic method leads to uterine transfer, obviously this will not always be the case. The patented method cannot be worked (performed) unless applied to a human embryo. Such a method supposes *embryo-use* with no guarantee that the method will be useful to the embryo subject to the test. If it is correct that any invention must be excluded where the technical teaching *presupposes* embryo destruction without claiming the step, it follows that any technical teaching of subject matter *leading to* or bringing about destruction of an embryo ought also to fall within the exclusion.

Quite exceptionally, the scope of art 6 (2) (c) was interpreted to extend to any use of a human embryo *in scientific research* thereby conflating research activity in stem cell science with industrial application. The Court reasoned embryo research 'cannot be separated from the patent itself and the rights attaching to it'.[48] The reasoning sits uncomfortably with the experimental use

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[45] Bot [113].
[46] A Odell-West, 'Preimplantation genetic diagnosis, the 'medical exclusion' and the Biotechnology Directive' (2007) *Medical Law International* 8 (3) 239.
[47] C Simon, 'To transfer or not to transfer …a mosaic embryo, that is the question' *Fertil Steril* 2017; 107, 1083.

[48] [43]-[44].

defence, which means that experimental research on the subject matter of the invention is not generally equivalent to commercial or industrial use.

On the basis of what turned out to be inaccurate scientific evidence placed before the Court, a *non-fertilized* ovum (a 'human parthenote') was a 'human embryo'. An embryo created by somatic cell nuclear transfer (SCNT) involving the transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryonic clone without the fusion of sperm and egg, also fell into the category of human embryo if the entity created can *'commence the process of development of a human being'*.[49] It is unclear whether this characterization includes human admixed embryos, which contain both human and animal material. The most common type of cytoplasmic hybrid embryos are created by adding the nucleus from a mature human cell such as a skin cell to an animal egg cell emptied of its nucleus using SCNT. These embryos are 99.9 per cent human. Nevertheless, a more pressing question for bioscience was that the *Brustle* judgment left open the question of duration, that is whether the process of development must continue for 40 weeks (the full gestation period for a human being) or whether development for one day might suffice. The answer came following a second referral to the CJEU on the meaning of 'human embryo' in art 6 (2) (c).

ISCO

The invention in ISCO concerned a method of producing pluripotent stem cell lines from a human parthenote. This is an embryo created from an ovum

[49] [36].

whose division and development is stimulated by a chemical process and not by fertilization with sperm.[50] The Comptroller of the UKIPO rejected the application on the basis of *Brustle* that as claimed the invention used human embryos. The scientific evidence was that human parthenotes couldn't develop to term because they lacked paternal DNA.[51] Thus in a second referral on the interpretation of 'human embryo' for purposes of art 6 (2) (c), the High Court (England and Wales) invoked a utilitarian calculus to balance *research in the field of biotechnology, which is to be encouraged by patent law* against *respect for the fundamental principles safeguarding the dignity and integrity of the person.* The High Court asserted that exclusion of human parthenotes from patentability struck 'no balance at all' between these objectives.[52]

The CJEU made no comment on the appropriateness of the proposed balancing test but instead reiterated the principle established in *Brustle* that in light of art 6 (2)(c), an unfertilized human ovum capable of commencing the process of development of a human being must be classed as a human embryo.[53] There was an important rider. Merely commencing the process was insufficient, the unfertilized human ovum must necessarily have *inherent capacity of developing into a human being*.[54] It followed that the *Brustle* classification of human embryo '… *does not apply if in light of scientific knowledge sufficiently tried and tested by medical science*[55] *… the embryo does not*

[50] C-364/13 *International Stem Cell Corporation v Comptroller of General Patents* (2014), hereafter "ISCO".
[51] [17] ISCO
[52] [19] ISCO
[53] [27] ISCO
[54] C-364/13 *International Stem Cell Corporation v Comptroller of General Patents* (2014) [28-29]
[55] [36] ISCO

have inherent capacity to develop into a human being, this being a matter for the national court to determine.'[56]

The CJEU was careful to distinguish between the patentability of an invention which involves a human parthenote incapable of commencing the process of development into a human being, from a parthenote that has been genetically manipulated to acquire inherent capacity.[57] The question whether an isolated pluripotent stem cell (presently incapable of commencing the process of development into a human being) falls within the meaning of 'human embryo' is also to be decided in light of prevailing scientific knowledge.

Nevertheless, it is difficult to explain a policy that underpins an EU-wide exclusion of hESC products or processes from patentability when according to the European Research Council, funding for human embryonic stem cell research is available within the ethical framework defined in the current Horizon 2020, and the European Group on Ethics in Science and New Technologies (EGE)[58] as mentioned earlier, have expressed the opinion that patenting inventions *using stem cells from human embryonic origin* to create genetically modified stem cell lines, or specific differentiated stem cell lines for specific therapeutic or other uses, is ethically acceptable.[59]

At the EPO

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[56] [38] ISCO
[57] ISCO [35-36]
[58] Established to advise the European Commission on all ethical aspects of biotechnology pursuant to art. 7 of the Biotechnology Directive.
[59] EGE Opinion no. 16, Ethical aspects of patenting inventions involving human stem cells, 7 May 2002, para 2.4.

According to their raison d'etre patent offices operate a presumption of patentability. In this, the EPO is no exception. Exceptions to patentability are construed narrowly giving effect to the EPC's underlying objective of establishing a comprehensive patent protection between the contracting states.[60] The rationale for narrow interpretation reflects the Roman law principle *singularia non sunt extendenda* applied in EU law according to which rules that provide for exceptions must be interpreted strictly in order to preserve the effectiveness of the general rule from which they derogate.[61]

Morality jurisprudence in EPO patent law has developed three distinct approaches: one to inventions in general, another to animals in the field of biotechnology and a third to inventions involving human biological material. We are concerned with the latter, though a brief discussion of the jurisprudential approaches is instructive to the debate.

The orthodox (i.e. narrow, strict) approach to exclusions requires that patent protection be denied pursuant to Art. 53(a) EPC only where the intended exploitation i.e. the avowed use indicated in the patent would infringe *ordre public* or morality.[62] If a non-infringing use is possible, the patent may otherwise be granted.[63] Supporting evidence of immorality and/or breach of *ordre* public at the date of filing must be adduced, the burden of which has been difficult to discharge in art 53(a) cases before the

[60] T 866/01 *Euthanasia Compositions*/ MICHIGAN STATE UNIVERSITY (2005) at 5.2 of the Reasons.
[61] Case T-124/14 *Republic of Finland v European Commission*
[62] *see* G 1/98, Reasons 3.3.3.
[63] T 866/01 *Euthanasia Compositions*/ MICHIGAN STATE UNIVERSITY (2005)

EPO. Economic or religious arguments are, 'of no assistance since no single such basis represents an accepted standard in European culture'.[64] Opinion poll evidence is not considered probative.[65] If there is no evidence to the tribunal's satisfaction, the "classic" art 53(a) EPC test cannot be applied[66] and objection on this ground must fail.

While morality was always *'… the basis for the inclusion of extra-legal principles of ethics in the law'*,[67] EPO caselaw has interpreted morality and *ordre* public as conceptually confined to ethically based rules, 'reflecting basic values prevailing in society and trade':[68]

> *'The legal approach based on morality for the EPC can be found in the concepts of the European cultural and legal systems. Morality constitutes actual ethically-based norms of behaviour that have become socially binding through being generally accepted. The exploitation of an invention only infringes morality if it is regarded as reprehensible by society in general or at least by the trade concerned'.* [69]

This built upon the theme in T356/93 *Plant Cells*/ PLANT GENETIC SYSTEMS in which it held that 'a fair test to apply is to consider whether it is probable that the public in general would regard the invention as so abhorrent that the grant of patent rights would be inconceivable'. Ideas in

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[64] T 315/03 HARVARD Reasons, section 10.10.
[65] T 356/93 PGS OJ EPO 1995, 545, Reasons, paragraph 15, followed in T 315/03 HARVARD.
[66] T 356/93 PGS OJ EPO 1995.
[67] T 866/01 *Euthanasia Compositions*/ MICHIGAN STATE UNIVERSITY (2005) at 6.12 of the Reasons.
[68] T 866/01 *Euthanasia Compositions*/ MICHIGAN STATE UNIVERSITY (2005) at 6.9 of the Reasons.
[69] 866/01 *Euthanasia Compositions*/ MICHIGAN STATE UNIVERSITY (2005) at 6.12 of the Reasons.

ethics that lead to norms of behaviour do not necessarily constitute morality and may even conflict. Medical ethics may dictate that a doctor cannot resuscitate a patient who has expressed the wish[70] not to be resuscitated; although her own morality may be to intervene and treat. Interpretation of morality for purposes of the exclusion in patent law can have no room for reactive attitudes such as abhorrence.[71] To reject the grant of a patent on the basis of an appeal to abhorrence or reprehensibility without moral reasoning is an appeal to bare prejudice.

Rule 28 (d) EPC Transgenic Animals

During revision of EPC 1973,[72] art 6 of the Directive was transposed as rule 28 EPC. In respect to animals the case law has developed a two-step approach to an art 53(a) EPC objection. The first inquires whether the claimed subject matter falls within the excluded category under Rule 28 (d) EPC.[73] If so, it must *ipso facto* be denied a patent under Article 53(a) EPC, no further deliberation is necessary.

A biotechnology invention that does not so fall, must be considered further under Article 53(a) EPC.[74] A so-called "real" or "classic" art 53(a) EPC objection,[75] it must be shown that commercial exploitation of the invention falls short of ethically established norms of vital significance, the binding

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70 In lawful and ethical circumstances.

71 *Guidelines for Examination in the EPO* (2015) following T356/93 *Plant Cells*/ PLANT GENETIC SYSTEMS (1995).

72 G 2/06 *Primate Embryonic Stem Cells*/ WISCONSIN ALUMNI RESEARCH INSTITUTE (2009) Reasons, section 16.

73 These correlate to Directive 98/44/EC art. 6 (2)(a)-(d).

74 T 315/03 HARVARD Reasons, section 6.

75 T 315/03 HARVARD.

force of which are generally accepted and recognized within EU societies.[76] This calls for evidence to be led that proves existence of the "norm" and breach of that norm as a result of commercial exploitation of the invention in issue. Rule 28 (d) prohibits the grant of a patent for any process that genetically modifies an animal likely to cause suffering without any substantial benefit to man including animals resulting from such processes. If an invention relating to a transgenic animal has withstood this test because it is concluded that a balance is struck between likely suffering and likely substantial medical benefit, the "classic" art 53(a) EPC test must be applied in a second line of defence against possible breaches of morality or *ordre* public. The "classic" approach requires a balancing test for biotechnology so that the invention's usefulness to mankind is "carefully weighed" against possible risks to the environment, and animal suffering, and any other factors suggestive of an *accepted standard of behavior in European culture* that commercial exploitation of the invention would breach.[77]

The requirement for a *multi-jurisdictional conception of morality* at the EPO is especially demanding. It is increasingly difficult to build consensus on what may be considered 'ethical' as society becomes more plural and culturally diverse. Widespread agreement across member states is inversely proportionate to the controversy of the subject matter. By contrast, morality for purposes of the Directive corresponds to ethical and moral principles recognized *in a member state*.[78] Establishing evidence before the EPO has often proved a monolithic task, with few art 53 (a) objections succeeding. This is not

[76] T 315/03 HARVARD Reasons, section 10.1.
[77] T 866/01 *Euthanasia Compositions*/ MICHIGAN STATE UNIVERSITY (2005) at 6.12 of the Reasons.
[78] Recital 39.

the case where fundamental rights are in play[79] to which we now turn.

Inventions involving human biological material

The first significant judgment on the patentability of inventions using human embryos was G 2/06 *Primate Embryonic Stem Cells*/ WISCONSIN ALUMNI RESEARCH INSTITUTE (WARF). The Enlarged Board of Appeal (EBA) rejected the usual approach to the morality exclusion and instead applied *mutatis mutandis* general rules for *treaty* interpretation[80] that require terms to be given their ordinary meaning in context and light of the treaty's object and purpose, including the preparatory documents.[81] The reason for this unprecedented derogation from a narrow construction of an exclusion rule was the fundamental principle of human dignity was engaged. For inventions involving human biological material, higher-ranking norms constitutive of human[82] and civil rights such as those guaranteed by international treaties and national constitutions, shape the concepts of art 53(a) EPC morality and *ordre* public against which the effect of commercial exploitation must be considered.[83] The EBA declared the relevant higher-ranking norm for Rule 28 (c) EPC the inviolability of human

[79] See T0149/11 STORK PMT (2013).
[80] Arts. 30-31 of the Vienna Convention on the Law of Treaties.
[81] WARF section 16 of the Reasons.
[82] Such as *The Charter of Fundamental Rights of the European Union* (Official Journal of the European Communities C 364/1 of 18 December 2000) and *Convention for the Protection of Human Rights and Fundamental Freedoms*, Rome 1950.
[83] T 0149/11 STORK PMT (2013) at 2.5 of the Reasons.

dignity,[84] in a moral leap that supposed this applied to the human embryo as defined.

The appellants in the WARF case submitted that the *absence* of a constitutional tradition embodying fundamental rights common to the member states that a pre-embryo ("one less than 14 days old") should *not* be used for stem cell research meant there was no reason to bar patenting of use to extract a few cells in accordance with usage in the medical field.[85] The EBA summarily dismissed this point, declaring there was '*no room for manoevre*' as to the ambit of art 53(a) EPC in conjunction with rule 28 (c) to accommodate this or other arguments as to whether the standard of morality ought to be European or not, whether it matters if embryonic stem cell research is allowed in certain EU countries, or whether the benefits of sharing the invention for humanity should be balanced against the prejudice to the embryo[86] (the utilitarian calculus hitherto applied by the EPO in art 53(a) EPC cases).

While a two-step approach to a morality or *ordre* public objection is established practice at the EPO for rule 28 (d) EPC in respect to transgenic animals, this approach for rule 28 EPC cases involving human biological material is debatable. Consider an invention that "uses [parthenogenic] embryos", to employ the language of the exclusion. Such "use" escapes exclusion under Rule 28 (c) EPC as the embryo *lacks inherent capability of*

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[84] G 2/06 *Primate Embryonic Stem Cells* / WISCONSIN ALUMNI RESEARCH INSTITUTE (2009).
[85] G 2/06 *Primate Embryonic Stem Cells* / WISCONSIN ALUMNI RESEARCH INSTITUTE (2009), section VI.
[86] G 2/06 *Primate Embryonic Stem Cells* / WISCONSIN ALUMNI RESEARCH INSTITUTE (2009) Reasons, section 31.

developing into a human.[87] In ISCO, the CJEU did not refer to further examination under art 6 (1) Directive as a second line of defence against potential breaches of morality or *ordre* public. However, if the second step were to be followed at the EPO, this would involve application of the classic art 53(a) EPC test to balance *benefit* of the invention for humanity against (for example) *prejudice* to the human parthenote;[88] that is whether or not for some plausible ratio of units of measure a comparison of utilities between benefit of the invention for humanity against prejudice to the human parthenote would lopsidedly favour parthenogenetic embryo use.

A utilitarian calculus is more inconsistent with the dignitarian approach adopted by the Enlarged Board of Appeal for inventions that "use human embryos" because if transferred to a uterus, parthenogenetic embryos are observed to develop to fetal stage, although further development is compromised by an underdeveloped placental system that prevents normal gestation.[89] The commercial use of parthenogenetic embryos beyond 14 days when neural pathways underlying pain sensation develop, may cause suffering to be experienced by the organism that is comparable to a fertilized human ovum at the same stage of development. The human parthenogenetic embryo, falling short of *"inherent capacity of developing into a human being"* is beyond the reach of the step 1 morality exclusion and must be assessed according to the classic art 53(a) EPC utilitarian test. Critically, human dignity is not engaged but can it be said that parthenogenetic suffering is morally

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[87] C-364/13 *International Stem Cell Corporation v Comptroller of General Patents* (2014) [28-29].
[88] Harvard
[89] ISSCR Guidelines for Stem Cell Research and Clinical Translation, 12 May 2016.

different to that of a fertilized human embryo at the same stage of development?

While it is not the role of patent law to regulate biomedical research, one way round this unedifying possibility would be for subject matter that involves use of an embryo *regardless of the derivation method* to be subject to a new conception of morality and *ordre* public that imports the 14-day rule, prescribed in the International Society for Stem Cell Research (ISSCR) guidelines (2010).[90] According to which after 14 days, all embryonic material would be automatically excluded under art 53(a) EPC 2000.

The disputed ethical acceptability of embryo research and evidential difficulty of establishing an *accepted standard of behavior in European culture according to* a *multi-jurisdictional conception of morality* at the EPO renders the "classic" utilitarian test ethically inadequate for non-fertilised embryos created by new technologies. Where evidence cannot be adduced, the balancing test cannot be applied and the invention must (if otherwise patentable) proceed to grant. The use of a parthenogenetic embryo in a patented invention beyond 14 days of development could otherwise be patented, contrary to widely shared ethical principles in science and medicine[91] that strictly upholds the 14-day rule in stem cell research.

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[90] Recommendation 2.1.3.3 (a).

[91] Nuremberg Code, 1949; Department of Health, and Education and Welfare, 1979; European Science Foundation, 2000; Medical Professionalism Project, 2002; Institute of Medicine, 2009; World Medical Association, 2013.

The 14-Day Rule

We have seen that the courts interpret the 'human embryo' as fully human at the zygote stage and therefore *owed an absolute duty of protection* according to the principle of human dignity from being *used* in an industrial or commercial context, including for research or its clinical translation. The rationale is that *any* use would hurt the principle of human dignity enshrined in EU law.

This prohibition, twice interpreted by the highest international appellate courts for patent law, presupposes two things. First, that a reasonably clear conception of human dignity exists in this context, which I suggested earlier doesn't.[92] Second, that each embryo lawfully donated to research in accordance with consent procedures required by the HFEA *would otherwise* be implanted into a *willing* uterus. For without this certainty there can be no new person. Kingma puts it this way:

"*A 14-day embryo in a petri-dish - which has passed the stage of being able to be implanted in a womb - does not have the potential to become a human being. Just as a spark in the Australian Bush is a potential fire; a spark on the North Pole is not. If the moral status of the embryo derives from being a potential human then, on this strong claim, only the embryo in a willing womb has moral status*".[93]

For Kingma this lends support to the argument that ethical deliberation of a "research" embryo must be distinguished from an embryo destined for

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[92] See C McCruddon, Human Dignity and Judicial Interpretation of Human Rights' EJIL (2008) 19 (4), 655 - 724.
[93] E Kingma, '*Moral status and the properties of the embryo*', in Nuffield Council on Bioethics, 'Human Embryo Culture' Report (2017), p 73.

implantation. The difficulty even so is that not all embryos marked for implantation are in fact transferred. The "parental project" (an expression used by HFEA) for which the embryos are created may complete before all are used. Some may be visibly poor quality and destroyed. Others intended for transfer may be deprioritized, and/or destroyed following PGD or PGS. Even if an embryo is transferred selective reductive abortion may be recommended by the ART practitioner in an effort to improve the outcome of pregnancy, which may be done around 12 weeks of gestation.[94] Contrary to the (*Brustle*/WARF) dignitarian view of the embryo's status, a *duty to protect* cannot exist in absolute form given that even a viable fetus can be aborted.

The regulation of stem cell research in England and Wales does not recognise the embryo's status as fully human and protected by the principle of human dignity.[95] This is not to suggest that stem cell research is a moral wild west with gun-slinging cowboys and dastardly outlaws. On the contrary, its regulation does not suffer lack of stringent ethical oversight. The approach according to the HFEA framework instead requires 'respect for the *special status* of the embryo'.[96] This *special status* prohibits as unethical keeping the embryo in culture beyond 14 days (or upon emergence of the primitive streak, if that happens first). Unlike the principle of human dignity interpreted in WARF and *Brustle* that applies at all stages of embryo formation and development to protect it from harm, the 14-day rule does not protect the

[94] DoH&SC, 'Abortion Statistics, England and Wales: 2017'. In 2017 there were 111 selective reduction abortions in England and Wales.
[95] See HFEA Code of Practice 9th edition, with which licensed centres must comply. The HFEA has a duty to promote compliance with the Act and Code of Practice.
[96] Regulatory Principles (Version 1.0) in Human Fertilisation and Embryology Authority, Code of practice (9th ed) 2018.

embryo's development or its integrity at all. Rather the rule is triggered by biological development, a point after which sentience becomes possible[97] and an ethical line transgressed unless the embryo in issue *is destroyed*. Although the ability to tie moral evaluations to developmental markers is disputed,[98] the 14-day rule has statutory force in England and Wales and is adhered to by the international bioethics community, clinicians, scientists, government officials and industry.[99] The 14-day rule is also upheld by the National Institute of Health's Human Embryo Research Panel and has been implemented in many countries around the world, making it "one of the most internationally agreed rules in reproductive science and medicine to date".[100]

The European Group on Ethics in Science and New Technologies (EGE) was set up to advise the European Commission on all ethical aspects of biotechnology.[101] Between 2000-2002 it met with Members of the European Parliament, jurists, philosophers, scientists, representatives of industries, representatives of religions, patients' associations and of international and European organisations (UNESCO, Council of Europe, WTO, WIPO and the EPO) to look at ethical issues around patenting inventions involving human

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[97] Appleby and Bredenoord assert no functional neural connections or sensory systems exist in the embryo at 14 days. JB Appleby, AL Bredenoord, 'Should the 14-day rule for embryo research become the 28-day rule? EMBO Molecular Medicine (2018) 10:e9437, 2.

[98] For example, that moral value should be "*far more epistemologically complex than mere developmental or biological markers to take account of notions of extrinsic value such as that derived from various environmental or contextual factors and symbolic value*" Nuffield Council on Bioethics, *Human Embryo Culture Workshop Report* (2017), p 43.

[99] Key ethical arguments underpinning the 14-day rule and whether there might be reasons to revisit the statutory rule are discussed in Nuffield Council on Bioethics, *Human Embryo Culture Workshop Report* (2017).

[100] JB Appleby, AL Bredenoord, 'Should the 14-day rule for embryo research become the 28-day rule? EMBO Molecular Medicine (2018) 10:e9437, 1.

[101] Directive 98/44/EC, art 7.

stem cells.

Honing in on the Directive's exclusion of commercial uses of human embryos, the wording of which leaves open precisely *which* embryos are excluded, and whether cells obtained from *donated embryos* might be patentable, it was considered appropriate to open these questions in light of the promise of stem cell research (i) in therapy of degenerative diseases and injury (ii) for studying fundamental processes of human development (iii) for toxicological testing and drug design, and (iv) the fact that the state of the art at the time of drafting the Directive could not have taken these questions into account.[102] Expert hearings followed, with regard to the full panoply of international laws and conventions, including ethics bodies' opinions. Human dignity (art 1) and right to integrity of the person (art 3) were taken into account with freedom of research (art 13)[103] and art 17, which provided that "intellectual property is protected".[104]

The Group identified the basic ethical dilemma as between encouraging scientific progress to benefit healthcare on one hand and impairing access to health care due to license fees on the other, therefore an appropriate ethical balance between investor and society interests was called for. It was the Group's considered opinion that to forbid patenting of stem cells or stem cell lines would be "contrary to the EU choices as expressed in the Biotechnology Directive"[105] and cause "a major slowing of this research field except in case of

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[102] EGE Opinion no. 16, ethical aspects of patenting inventions involving human stem cells, 7 May 2002, para 1.2.1.
[103] Also, art. 12(b) Universal Declaration on the Human Genome and Human Rights, which proclaims freedom of research as "part of freedom of thought".

[104] Charter on Fundamental Rights of the European Union (2000).
[105] EGE Opinion no. 16, ethical aspects of patenting inventions involving human stem cells, 7 May 2002, para 2.1.

a very unlikely large public investment, contrary to public and especially patients' interests". [106] On balance, there *was no specific ethical obstacle* involved in patenting stem cells *from human embryonic origin* for specific therapeutic or other uses.[107] Neither was any ethical objection identified to the patenting of modified stem-cell lines (e.g. by *in vitro* treatments or genetic modification).

Therefore, by imparting full moral status to the single cell human embryo in line with a theory of zygotic personhood (which implies a presupposition about the beginning of life) the respective courts in *Brustle* and WARF significantly departed from the EGE's view, arriving at a conclusion about the embryo's status that sits uncomfortably with EU rules on stem cell research funding.

EU Stem Cell Funding

The EU Regulation establishing Horizon 2020 provides that research on human embryonic stem cells can be financed depending on the scientific proposal and the legal framework of the Member States involved.[108] In April 2014 the European Citizen's Initiative (OneofUs) proposed legislative amendments to stop this by excluding from European funding research activities that 'destroy human embryos, including those aimed at obtaining stem cells, and research involving the use of human embryonic stem cells in subsequent steps to obtain them'.

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[106] EGE Opinion no. 16, ethical aspects of patenting inventions involving human stem cells, 7 May 2002, para 2.1.
[107] EGE Opinion no. 16, ethical aspects of patenting inventions involving human stem cells, 7 May 2002, para 2.4.

[108] Regulation (EU) No 1291/2013 Of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020), art. 19(4).

The Commission elected not to uphold the request because[109] it considered the Horizon 2020 provisions to be fully accord with EU Treaties and the Charter of Fundamental Rights of the European Union, specifically human dignity, right to life and right to integrity of the person. The Commission stated destruction of human embryos is not funded, although research *subsequent to the establishment of human embryonic stem cell lines* will continue to be funded because 'ethical considerations, potential health benefits and the added value of support at EU level for all types of stem cell research' are taken into account.[110]

To be clear, embryonic stem cell lines cannot be created without destroying an embryo. The Commission's position on Horizon 2020 funding is wholly inconsistent with that of the CJEU in *Brustle*, where the doctrine of *complicity* predicated on the dignity of the embryo serves to exclude human embryonic stem cell lines from patentability.[111]

My central theme is that EU legal institutions and Parliament (HFEA) cannot rationally prohibit the use of embryos in patented innovation *and* permit as well as fund embryonic stem cell research that "uses" embryos within the meaning of complicity established in WARF *and* permit commercial fertility services, such as IVF and PGD the bulk of which is done in the industrial

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[109] EU Commission, Memo Brussels 28 May 2014 Request to change financial regulation, the Horizon 2020 regulation and development cooperation instrument (DCI) regulation. Details at http://www.oneofus.eu/

[110] Communication from the Commission on the European Citizens' Initiative "One of Us" Com (2014)355 final, para 3.2.

[111] Prof G Virt, while agreeing with Opinion no. 16 EGE, expressed a dissident opinion that derivatives of destroyed embryos should not be permitted to be patented as this contradicts the dignity of the embryo as a human being with a derived right to life (at p 19).

fertility sector.[112] That the sector provides the largest source of embryos used in stem cell research only serves to emphasise the irrationality.

Against Commodification?

'All such biomedical research is a collective effort that depends on the contributions of many individuals. Each may also be working toward different goals. When this collective effort works well, the social mission of clinical translation is achieved efficiently alongside the private interests of its various contributors'

ISSCR Guidelines for stem cell research and clinical translation (2016).[113]

Such "private interests" include intellectual property capture for the commercial sector, likely to be doing the investing. Although the impact of patents on science and the issue of the anticommons has been an area of concern, the Royal Society has long stated its support of patenting innovation in the area of human stem cell science, '*provided proper account is taken of public concerns*'.[114] Where the government, insurers or patients elect to fund clinical development to meet an unmet medical need the ISSCR guidance states emphatically, '*it is a matter of social justice that the costs of proving the safety and efficacy of a medical intervention be borne by entities that are expressly privileged to profit when such interventions are marketed*'.[115]

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[112] M Brazier, 'Embryos' "rights": abortion and research' in *Current Legal Problems* (ed. M Freeman) (1988) London, Stevens & Sons, 9-22, 19.

[113] ISSCR Guidelines for stem cell research and clinical translation (2016), p 4

[114] The Royal Society, Keeping Science Open: the effect of intellectual property policy on the conduct of science (2003), para 3.20. Available at https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2003/9845.pdf (accessed July 2019).

[115] ISSCR Guidelines for stem cell research and clinical translation (2016), p 5

Contractual arrangements to facilitate IP capture may mean that research findings must be kept confidential to protect novelty for longer periods than researchers might prefer. Seeking a compromise, the International Society for Stem Cell Research (ISSCR) guidelines provides that '*a reasonable delay is permissible to secure appropriate protections of intellectual property'*. Arrangements for the disposition of intellectual property must involve '*best efforts to preserve nonexclusive access for the research community … without undue financial constraint*'.[116] In the UK, it is expected that any patents arising from stem cell research and development activities funded by the Medical Research Council (MRC) or Biological Sciences Research Council (BBSRC) carried out pursuant to the UK Stem Cell Bank's operation, are assigned to MRC for the purposes of protection and exploitation.[117] What all this indicates is that patenting innovation arising from embryonic stem cell research is an anticipated feature in the field.

So it is interesting to investigate whether the exclusion from patentability of subject matter that commercially uses human embryos is meeting legislative objectives *in practice*? To gain a current snapshot, searches were conducted for patents granted or last renewed at the UKIPO between 2018-2019 involving use of human embryos. This revealed two UK patents[118] directed to inventions that claim the use of human pluripotent stem cells obtained from a human embryo (blastocyst), or an established human ES cell line such as Wicell or the UK Stem Cell Bank. Cells that are sourced from a human ES cell line (as

[116] ISSCR Guidelines, p 12, recommendation 2.3.6.
[117] Medical Research Council (MRC) *Code of Practice for the Use of Human Stem Cell Lines, Version 5* (2010) para 11.2.
[118] Publication nos. GB2483617, GB2485113.

opposed to a human iPS line) originate from a human embryo (usually a blastocyst).[119] The principle of complicity established in WARF precludes claims directed to use of such cells.

Searches were also undertaken using the Worldwide EN database for the period 2018-2019 to capture a snapshot of patents filed in EPC countries for inventions that involve use of human embryos,[120] where "use" as I argue above includes methods that (i) *discriminate* between embryos, as opposed to inventions for therapy or diagnosis applied to the embryo that are useful to it[121] such as preimplantation diagnosis[122] and preimplantaion screening[123] (ii) "use" in IVF[124] which I suggest is comparable to commercial use in patent law, and (iii) "use" to develop new human ES cell lines.[125]

The effect of the ban on patenting inventions that use embryos or their derivatives has not been investigated in the UK, although one recent report on the competitive global market for human embryonic stem cell research finds that the international divide on patentability has damaged hESC research in Europe.[126] Companies in the field often build their business model

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[119] https://www.nibsc.org/science_and_research/advanced_therapies/uk_stem_cell_bank/due_diligence.aspx

[120] Using the term "human embryo" in a search of a worldwide database covering 100+ countries revealed 75 filed patent documents for the period Mar 2018 - Mar 2019. Not all of these involve use of a human embryo.

[121] Recital 42 Directive 98/44/EC.

[122] See e.g. Published patent application nos. RU2659152, RU2671156 "*PGD allows you to choose from all embryos obtained by IVF, those that do not carry the mutation that causes the (type 1 spinal muscular atrophy) disease*".

[123] See e.g. Published patent application no. CN108588202.

[124] See e.g. Published patent application nos. CA3035055; RU2657769; CN108885649, KR20190020638.

[125] See e.g. Published patent application nos. RU2663339, AU2019200513.

[126] Global Human Embryonic Stem Cell (hESC) Research Industry (2018) Report ID 4778749 available at: https://www.reportbuyer.com/product/4778749/global-human-embryonic-

around a particular technology such as a new tool for disease modelling and toxicity testing. Patent acquisition is central to the competitiveness of these businesses. As the competitive global market for human embryonic stem cell research is expected to grow at a compound annual growth rate of 36.52 per cent between 2017 - 2021,[127] the absence of patent protection for innovation that involves *any use, ever* of a human embryo is likely to be a disadvantage.

Schism in the ethicality of "use" of a human embryo in a commercial context emerges

And so a schism concerning the ethicality of "use" of a human embryo *in a commercial context* emerges. Any use in a patented method is declared to be ethically unacceptable constituting a breach of human dignity whereas any use including destruction pursuant to a contractual obligation for fertility services is ethically acceptable. Despite the different commercial contexts in which the embryo is/ would be used, a logical distinction is difficult to discern. Whether the respective policies can co-exist is a question of moral philosophy, beyond the scope of this paper. But the conflicting notions of the embryo's *status* represented in the HFEA regulatory framework on one hand, and according to patent jurisprudence on the other, are rationally unsustainable.

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stem-cell-hesc-research-industry.html. See ALLEA 'Patenting Inventions Involving Human Embryonic Pluripotent Stem Cells in Europe', asserting European researchers at a competitive disadvantage following WARF (2011), available at: http://www.allea.org/wp-content/uploads/2015/09/ALLEA-SC-IPR-statement-Stem-Cell-Patenting-2011-final.pdf (accessed July 2019).

[127] https://investingnews.com/daily/life-science-investing/genetics-investing/top-stem-cell-nasdaq/

Part 2

It was noted earlier the Directive's mandate that patent law be applied in a way that respects morality and fundamental principles recognized in EU law *safeguarding dignity and integrity of the person*.[128] But what does the concept of *dignity* require in the context of the exclusion of industrial and commercial uses of the embryo? Can it be argued that the principle precludes the 14-day rule from being incorporated as an extra-legal ethical principle in patent law? I will suggest not.

Dignity and the fetus from the human rights perspective

Dignity, like the question of the embryo's moral status, is an example of an important but deeply contested concept. In the human rights context, McCruddon's leading research on dignity reveals '*little common understanding of what dignity requires substantively or across jurisdictions*' beyond a basic minimum core.[129] This core claims that each human being has intrinsic worth merely by being human and that some forms of treatment are inconsistent or required by this intrinsic worth.[130] Yet a lack of consensus politically or philosophically on how these claims ought to be understood contributes to the existence of several conceptions of human dignity that '*differ*

[128] Directive 98/44/EC, recital 16.
[129] C McCruddon, 'Human Dignity and Judicial Interpretation of Human Rights' (2008) EJIL 19, 655 - 724, p 655.
[130] A third element of this core of less significance here is 'recognizing individual intrinsic worth requires that the state should be seen to exist for the sake of the individual human being and not vice versa'. C McCruddon, 'Human Dignity and Judicial Interpretation of Human Rights' (2008) EJIL 19, 655 - 724, p 679.

significantly'.[131] For example, some see no role for morality in dignity only human existence[132] while others do, particularly in respect to the substantive scope of human rights.[133] In patent law, the substantive scope of the morality and *ordre* public provisions is shaped by norms constitutive of civil and human rights such as dignity.

When it comes to who should make a decision whether or not to accord dignity to an entity, or who should decide whether the balance between dignity and other values is appropriate, McCruddon observes a '*radical difference*' between jurisdictions - with the '*greatest unresolved difference being the question whether a human fetus has dignity*'.[134]

So much for the hope of shedding some light on dignity from the human rights context.

The human embryo's status

The status that ought to be accorded the human embryo is even today, as Brazier argued many years before a circular debate.[135] Whether or not humanity is simply a rational animal whose rationality alone commands respect, or a divine creation, can be neither proved nor disproved:

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[131] C McCruddon, 'Human Dignity and Judicial Interpretation of Human Rights' (2008) EJIL 19, 655 - 724, p. 680.
[132] C Dupre, The Age of Dignity: Human Rights and Constitutionalism in Europe (2015) Oxford: Hart Pub p 21.
[133] G Letsas, 'Strasbourg's interpretative ethic: lessons for the international lawyer' (2010) 21 Eur J Int L 509 at 531.
[134] C McCruddon, 'Human Dignity and Judicial Interpretation of Human Rights' (2008) EJIL 19, 655 - 724, p 708.
[135] See, M Brazier, 'Embryos' "rights": abortion and research' in *Current Legal Problems* (ed. M Freeman) (1988) London, Stevens & Sons, 9-22, 14.

It is a debate incapable of resolution in a form which could provide definitive legal criteria on which to base laws on either abortion or [embryo] research. For the chasm which separates the participants is unbridgeable.'[136]

The question whether it is the emergence of certain features or intrinsic properties that give rise to moral status is hotly debated.[137] In respect of the latter, one view is that the embryo's moral status is linked to its *potential* to become a human being pursuant to *intrinsic* properties alone.[138] Others consider embryonic *potentiality* requires *extrinsic* features to be taken into account, a 'willing' womb into which it must be transplanted by day 14, the view I have taken in this paper. Although many countries permit embryonic stem cell research[139] one looks in vain for consensus on these questions.

Respect for Life

Methods that imply destruction of human embryos resuscitate a long-fought battle over the principle of *respect for human life*. For example some people hold the view that to destroy human embryos in order to obtain embryonic stem cells following elective abortion or from surplus IVF embryos is ethically unacceptable.[140] Others express the view that it is morally permissible to

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[136] M Brazier, 'Embryos' "rights": abortion and research' in *Current Legal Problems* (ed. M Freeman) (1988) London, Stevens & Sons, 9-22, 13.
[137] 'Even within those groupings that hold with a particular account of moral status, for example personhood, we see much disagreement about the details': C Elves and S McGuinness, *The statutory time limit for maintaining human embryos in culture: Background Paper* in: Nuffield Council on Bioethics (2017) 'Human Embryo Culture' report, paragraph 13.
[138] C Elves and S McGuinness Background paper, para 17.
[139] E.g. Australia, Belgium, Brazil, Canada, China, Czech Republic, Denmark, France, Germany (…) The Department of Health, UK Stem Cell Initiative - global positions in stem cell research, available at http://www.dh.gov.uk.
[140] See J R Meyer, 'Human embryonic stem cells and respect for life' (2000) *J Med Ethics* 26, 166-170.

decline transfer of *in vitro* embryos and based upon this permission and the duty of beneficence, there is justification for using human embryos in the service of humanitarian ends.[141] The International Bioethics Committee perhaps best sums up the polar views:

'*On the one hand, there are those who support the argument that the threshold of the 'right to life' is reached only at some point of the development of human life, depending on several considerations on the progressive acquisition of essential characteristics, traits, and abilities as well as the necessity to balance this principle with the one protecting the mother's self- determination. On the other hand, there are those who contend that unconditional respect is due from the very beginning, building on the observation that embryo development is an ongoing process as well as a strong notion of the sanctity of life. Even the most widespread religions do not share the same position.*'[142]

In patent law, the point at which human dignity is owed is the first stage of development of a human being. Thus the single-cell zygote is fully human, the dignity owed to this cell the same as that owed to you or I. For Hitchcock, this state of affairs is wholly unacceptable, who believes that the dignity of an actual person should take priority over that of a not-yet person:

'*The statutory purposes for licensing human embryo research are directed towards securing 'human dignity' of born human beings from the ravages and indignity of disease. Placing the dignity of pre-persons above that of actual persons*

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141 L Guenin, The Morality of Embryo Use (2008) Cambridge Uni Press.
142 International Bioethics Committee, 'Report on Updating reflection on the human genome and human rights' (2015) SHS/YES/IBC-22/15/2 REV.2 Paris, 2 October.

appears not only to be wrong legally, but unethical too'.[143]

While *Brustle* and *ISCO* are binding authority on EU national courts, whether the weight and legal status of the embryo's human dignity may be 'balanced' against other interests or trumped by other rights depends to some extent on where the case is brought. In Germany human dignity has a status superior to other human rights with '*no way to balance other legal interest*s', which is in contrast to France or Hungary, for example.[144] The statutory regulation of research using human embryos *balances* embryo use with factors such as societal benefit, its great therapeutic potential, with respect to a wide range of life-threatening diseases; an approach rejected outright by the Enlarged Board in WARF.

Even in ECtHR jurisprudence the question of the moral status of the human embryo and whether dignity applies, is unclear.[145] In *Parrillo v Italy* the Grand Chamber of the ECtHR adjudicated a complaint that under Italian law a woman was unable to donate her IVF embryos but obliged to keep them in a state of cryopreservation until their death. The applicant argued the legal restriction was contrary to the right to self-determination, relying on Article 1 of Protocol No. 1 of the Convention

'*Every natural or legal person is entitled to the peaceful enjoyment of his possessions. No one shall be deprived of his possessions except in the public interest and subject to the conditions provided for by law and by the general principles of international law*.'

[143] Hitchcock, Nuffield Council on Bioethics (2018)
[144] C McCruddon, Human Dignity, p 699.
[145] *Parrillo v Italy* [2015] ECHR

'Diametrically opposed' views about the status of the human embryo *in vitro*[146] were expressed, the Italian Government adamant that embryos cannot be regarded as "possessions" while Ms Parrillo submitted that embryos conceived by *in vitro* fertilisation could not be regarded as "individuals". If they were not implanted they were not destined to develop and be born, so that from a legal point of view they were "possessions".[147] In the separate opinions of the Court was some discussion of *Artavia Murillo et al. (*in vitro *fertilization) v Costa Rica* in which the Inter-American Court gave a ruling on the ban on *in vitro* fertilisation in Costa Rica, holding *inter alia*, that an embryo could not be regarded as a "person" within the meaning of Article 4 § 1 of the American Convention on Human Rights, protecting the right to life, conception occurring only from the moment the embryo was implanted in the uterus.[148] Ms Parrillo argued a right of ownership existed over her embryos, against which the State had imposed unjustified restrictions. In her view, the protection of the embryos' potential for life could not reasonably be invoked since they were destined to be eliminated.[149]

Having regard to the economic and pecuniary scope of Article 1 of Protocol 1 the court held that human embryos cannot be reduced to "possessions"[150] with the effect that that part of the complaint was incompatible *ratione materiae* with the provisions of the Convention.[151] It was therefore unnecessary

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[146] *Parrillo v Italy* [2015] ECHR at [214]
[147] *Parrillo v Italy* [2015] ECHR at [203]
[148] Judgment of the Inter-American Court of Human Rights in *Artavia Murillo et al. (*in vitro *fertilization) v Costa Rica* (preliminary objections, merits, reparations and costs), judgment of 28 November 2012, Series C No. 257.
[149] *Parrillo v Italy* [2015] ECHR at [204]
[150] Although the complaint based on Art 8 of the Convention was admissible, there had been no violation (16:1 votes).
[151] *Parrillo v Italy* [2015] ECHR at [216]

to examine the "sensitive and controversial question of when human life begins."[152]

Zygotic Personhood

' The human body exists, is formed and develops independently of the person who occupies it … contemporary science cannot tell us when the human person truly begins'.[153]

So mused Advocate General Bot in the *Brustle* case. Personhood, like autonomy or rationality, is a concept associated with normative notions of humanity. As discussed earlier, the exclusion from patenting of commercial uses of embryos bites as soon as the zygote is formed (the single-cell entity consisting of a fused ovum and sperm) as opposed to any later stage of development.[154] The definition promulgated by the courts is in line with a theory of zygotic personhood that sees the first stage of a *human being* as occurring upon creation of the zygote.

Probably the strongest of all faith arguments against embryo use, invoking the sanctity of life, is the Catholic Church. For Guenin, the Catholic Magisterium of the Holy See[155] is based on a theory of zygotic personhood: a

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[152] *Parrillo v Italy* [2015] ECHR at [214]
[153] Opinion of AG Bot in C-34-10 *Brustle v Greenpeace eV*, delivered 10 March 2011, [73 - 80]
[154] Brustle
[155] As set forth in the instructions of the Sacred Congregation for the Doctrine of the Faith.

zygote is *a new person* because fertilization forms a new genome.[156] Using a turn of phrase resembling that used by AG Bot above, the Magisterium reads:

'*… it is not up to biological sciences to make a definitive judgment on questions which are properly philosophical and moral such as the moment when a human person is constituted … even if a doubt existed concerning whether the fruit of conception is already a human person, it is objectively a grave sin to risk murder*.'[157]

According to zygotic personhood, as *possible* persons moral duties may be owed such as a duty of noninterference and a duty not to harm or kill. But nowhere does the case law seriously suggest that the embryo is an actual "person" for purposes of recital 16 of the Directive.

Duty of Beneficence

The International Ethical Guidelines for Biomedical Research Involving Human Subjects[158] is guided by three ethical principles: respect for persons,

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156 L M Guenin, p. 160.

157 Roman Catholic Magisterium of the Holy See as set forth in the instructions of the Sacred Congregation for the Doctrine of the Faith, *Declaration on Procured Abortion*, §§ 12-13 (a translation of which also appears in Ford 1988, pp 60 - 61), as reaffirmed in *Donum Vitae*, §I(I), cited in Guenin, p 160.

158 The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organisation established jointly by the WHO and Unesco in 1949. Like those of 1982 and 1993, the 2002 CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects.

beneficence and justice to research involving human subjects.[159] If it is accepted that we are not dealing with fully-fledged "persons", the principle of beneficence alone stands out.

The duty of beneficence is held in common across the range of leading moral views. *It is that we have a duty, insofar as we can do so without imposing an unreasonable burden upon ourselves or others, to contribute to the provision of assistance to those in need.*[160]

To obtain embryonic stem cells following from surplus IVF embryos is ethically unacceptable for some and no duty of beneficence attaches.[161] For others, society would suffer a significant opportunity cost if embryos that could have been used in an act of beneficence were instead disposed of, '*… to forego embryo use would be to forsake the opportunity to help another who suffers and yet 'not one more baby would be born.'*[162]

The role of "isolation" and dignity

Art 1 of the Universal Declaration of Human Genome and Human Rights[163] (UDHGHR) states "the human genome underlies the fundamental unity of all

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[159] See also the WHO publication "Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants", 2011. In 2003 the WHO had already approved the Guideline for Obtaining Informed Consent for the Procurement and Use of Human Tissues, Cells and Fluids in Research, which provides that monetary payment or other inducement for donating embryonic tissue for research is expressly prohibited.
[160] Guenin, p 47.
[161] J R Meyer, 'Human embryonic stem cells and respect for life' (2000) *J Med Ethics* 26, 166-170
[162] Guenin p. 48.
[163] Universal Declaration on the Human Genome and Human Rights by the General Conference of the United Nations Educational, Scientific and Cultural Organisation (Unesco) in 1997.

members of the human family, as well as the recognition of their inherent dignity and diversity"". This provision gave rise to '*the well-known definition of the human genome as "the heritage of humanity" in a symbolic sense, underlining the outstanding value of what should be protected and transmitted to future generations*'.[164] Although the international bioethics community stated in the strongest possible terms that convincing, powerful ethical grounds existed to exclude the human genome from patentability,[165] isolated DNA is patentable subject matter in EU/EPC contracting states, a feature that continues to excite incredulity among people today. If it is correct that DNA, the super-chemical underlying our human identity and conveyor of dignity, once *isolated from the human body or otherwise produced by means of a technical process* does not breach dignity if patented, might this rationale concerning human intervention (a technical process) apply to elements isolated from an embryo, where both embryo and stem cell are clearly outside its natural state? The legal answer is negative but it is a conclusion that does not logically follow.

Conclusion

On the basis that it is legitimate to incorporate extra-legal ethical principles into patent law, I have argued for an interpretation that incorporates the 14-day rule to permit "use" of donated IVF embryos in order to strike a finer balance between investor and society interests, presently skewed by the full

[164] International Bioethics Committee, 'Report on Updating reflection on the human genome and human rights' (2015) SHS/YES/IBC-22/15/2 REV.2 Paris, 2 October, p 26 para 107.
[165] Unesco International Bioethics Committee, Advice of the IBC on the Patentability of the Human Genome, Eighth session of Unesco (IBC), Paris, 12-14 September 2001.

moral status of the embryo bestowed by the convenient language of dignity.

The prohibition against inventions involving use of human embryos is out of kilter with the regulation of stem cell research that is ethically conducted according to the 14-day rule, the trajectory of stem cell science and its translation into new health care technologies for the clinical setting.

Patent law currently pays insufficient attention to the interest in preventing actual human suffering, to stimulate greater investment in stem cell innovation through the unrivalled incentivisation mechanism of the patent system. It does this by conceptualizing the zygotic embryo as equivalent in 'status' to a born human being to whom human dignity unequivocally applies. Moreover, it imposes this status to protect the dignity of a single-cell entity with capacity to develop into a human being, which cannot ever materialize. It cannot materialize because the embryo has been donated to scientific research in accordance with the right of the donor(s) to determine the fate of their embryo(s). At the same time the creation of embryos and their destruction is a regular occurrence in the HFEA-licensed clinics of the burgeoning industrial fertility sector. I have argued that the use of such cells according to the 14-day rule should be accommodated in patent law as a widely accepted, extra-legal ethical principle removing the doctrine of complicity and providing for the patentability of inventions that use such cells to benefit society, when those cells have been donated in accordance with the conscious and considered decision of the donor(s).