Commentary

European stem cell research in legal shackles

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Advances in stem cell biology have raised legal challenges to the patentability of stem cells and any derived technologies and processes. In 1999, Oliver Brüstle was granted a patent for the generation and therapeutic use of neural cells derived from human embryonic stem cells (hESCs). The patent was challenged and put before the European Court of Justice, which ruled that inventions involving the prior destruction of human embryos cannot be patented. The legal maneuvering around this case demonstrates that the future of stem cell-based patents in Europe remains unsettled. Furthermore, owing to the European Court's broad definition of hESC as 'any cell that is capable of commencing development into a human being,' novel technologies that could eliminate the need for hESCs, such as induced pluripotent stem cells (iPSCs), are at risk of being included under the same ruling. Advances in the *in vitro* development of germ cells from pluripotent stem cells may one day provide a direct developmental path from iPSC to oocyte and sperm, and, according to the European Court's reasoning, legally equate iPSCs with human embryos. In this review, we will briefly discuss the Brüstle v Greenpeace case and the implications of the European Court of Justice's ruling. We will identify potential risks for stem cell research and future therapeutics resulting from the broad legal definition of the human embryo. Finally, we will broach the current legal landscape, as this broad definition has also created great uncertainty about the status of human iPSCs.

The EMBO Journal (2013) 32, 3107–3111; doi:10.1038/emboj.2013.249; Published online 22 November 2013
Subject Categories: development; molecular biology of disease

Stem cells

Stem cells have two unique properties: self-renewal and the ability to develop into specialized cell types. On the basis of their developmental properties, two classes of stem cells are distinguished: adult stem cells and pluripotent stem cells. Adult stem cells maintain and restore specific tissues, such as bone marrow, liver, and muscle. Their developmental potential is restricted as they give rise to only the distinct cell types belonging to one specific tissue type.

Pluripotent stem cells, in contrast, have the ability to form all different cell types in the body. The first such stem cell cultures were established in 1980 by Gail Martin, Martin Evans and Matthew Kaufman (Evans and Kaufman, 1981; Martin, 1981), who discovered independently, that embryonic stem (ES) cells could be derived from pre-implantation murine embryos. These cultured ES cells—or ES cell lines—can be coaxed to form a variety of differentiated cell types *in vitro*, which, upon transplantation into a recipient host, can restore tissue function (Daley, 2012). The first human ES cell lines were created in 1998 by James Thomson at the University of Wisconsin, USA, and raised hopes of regenerative therapies, such as cell or tissue replacement (Thomson *et al*, 1998). Now, the first viable clinical applications of human pluripotent stem cells are starting to emerge (Hyun *et al*, 2008; Cyranoski, 2013).

The derivation and use of human ES cells is controversial because these cells are derived from pre-implantation human (blastocyst) embryos, and it involves the destruction of the embryo. This has generated intense societal and political discussion about the moral, ethical and legal aspects of deriving and using human ES cell lines in research and resulting therapeutic applications. A Nobel award-winning discovery recently resolved this ethical dilemma. In 2006, Kazutoshi Takahashi and Shinya Yamanaka created pluripotent stem cells from somatic cells (skin fibroblasts) through the ectopic expression of four transcription factors (Takahashi and Yamanaka, 2006; Takahashi *et al*, 2007a, b). These cells, called 'induced pluripotent stem cells' (iPS cells) are functionally identical to ES cells as they can generate virtually any cell type *in vitro* or *in vivo*. More importantly, the possibility of generating iPS cells from a patient's own cells alleviates the emotional and ethical issues associated with this type of research because no embryo is used in the generation of these cells.

Background of the Brüstle case

In 1997, Dr Oliver Brüstle, neuroscientist at Bonn University in Germany, filed a patent 'Neural precursor cells, method for the production and use thereof in neural defect therapy,' on the process of deriving neural precursor cells from ES cells for the purpose of transplantation therapy for neural defects. The patent was granted in 1999, but challenged in 2004 by

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Received: 30 August 2013; accepted: 4 November 2013; published online: 22 November 2013

Glossary

Parthenogenetic embryo: Embryo created from an unfertilized egg, which, after chemical activation, starts development. The parthenogenetic embryo contains a diploid genome with exclusive maternal contribution.

Androgenetic embryo: Embryo created through pronuclear exchange of fertilized oocytes, or through bispermic *in vitro* fertilization of enucleated oocytes. An androgenetic embryo contains a diploid genome with exclusive paternal contribution.

Teratoma: A teratoma is a tumour that contains differentiated derivatives of two and often all three embryonic germ layers.

Trophectoderm: The trophoctoderm is the tissue derived from the trophoblast; the outer layer of cells of the blastocyst embryo. After embryo implantation and gastrulation, the trophoctoderm will form most of the placenta.

Epiblast: Cells derived from the blastocyst inner cell mass that will develop into the embryo proper.

Greenpeace in the German Federal Court, and ultimately referred to the European Court of Justice (hereafter the European Court). The European Court ruled in 2011 that a patent application implies commercialization of the patented material and, since commercialization of human embryo-derived products is undesirable, patenting such products is not permissible. To prevent any possible ‘work-around’ to this rule, the European Court used an unusually broad definition of the human embryo as an entity that is ‘capable of commencing the development of a human being.’ This definition would include parthenogenetic and androgenetic embryos. While these do commence development and develop defined trophoctoderm and epiblast lineages and subsequent (early) germ layer determination, these are artificial structures, which cannot develop into viable embryos (see glossary box).

The legal trail

Brüstle’s patent claim includes isolated and purified neural precursor cells, the processes for their production from ES cells and the use of neural precursor cells for the treatment of neural defects. As such, it falls under the European Directive on Biotechnology (Directive 98/44/EC; hereafter the Biotech Directive), which was adopted in 1998 to harmonize the patentability of biotechnological inventions across all EU Member States. According to the Biotech Directive, the use of human embryos for industrial and commercial purposes is unpatentable. However, the Biotech Directive does not define ‘human embryo,’ and fails to qualify whether this term includes a pre-implantation embryo. Furthermore, the Biotech Directive does not specify the meaning of industrial/commercial use. Greenpeace’s lawsuit therefore claimed that the cells used by Brüstle would not be patentable because they originated from a human embryo.

Three key questions referred to the European Court

The German Federal Court deferred their judgement and asked the European Court to clarify three questions and specifically address the interpretation of the Biotech Directive: (1) for an interpretation of ‘human embryo’ in the Biotech Directive, which considers the use of human embryos for industrial and commercial purposes unpatentable but fails to qualify whether this includes pre-implantation

human embryos; (2) whether the ‘uses of human embryos for industrial or commercial purposes’ also includes the use of human embryos for scientific research; and (3) whether an invention is patentable if its purpose is not the use of the human embryo itself, but rather a derivative product that required the prior destruction of human embryos or a process that requires base material obtained by the destruction of human embryos.

With this last question, the European Court was asked, in essence, how far removed from embryo destruction a derived product/technology must be in order to be patentable? This question is central to the Brüstle patent, since an important application of hESCs is the design of experimental models for the development or testing of new pharmaceutical compounds. Since human neurons cannot be obtained and cultured from consenting adults or cadavers, the derivation from pluripotent stem cells is the only feasible experimental method for studying these cells. Furthermore, if neural progenitor cells derived from hESCs, or the methods for their derivation, cannot be patented, what about drugs that are developed using hESC-derived neurons?

The European Court’s judgement

The European Court stated that while the concept of a ‘human embryo’ is a sensitive issue in some Member States, it could not consider ethical questions. Instead, it declared that this concept must be broadly interpreted, in order to exclude patent possibilities whenever respect for human dignity could be affected (par. 34 of the judgement). Therefore, the central criterion for a ‘human embryo’ is that it should be ‘capable of commencing the process of development of a human being,’ regardless of its method of inception or ability to yield a viable fetus. This broad definition includes entities such as a non-fertilized human ovum into which a nucleus from a mature human cell has been transplanted (e.g., embryos generated through somatic cell nuclear transfer or androgenetic embryos); and a non-fertilized human ovum, whose development has been stimulated by parthenogenesis (par. 36 of the judgement) (for terms, see glossary box). Interestingly, the European Court defers to national courts the decision whether stem cells obtained from a human embryo at the blastocyst stage are patentable (par. 37 of the judgement). This is particularly odd, since most human ES cell lines available to date are derived from blastocyst-stage embryos, and it would therefore seem that the status of the blastocyst embryo and derivative stem cell lines is most relevant.

In addition, the European Court argued that granting a patent claim implies commercial application of the research, and therefore patent restrictions apply to scientific research (par. 40–41 of the judgement). Of note, the European Court did clarify that the Biotech Directive ‘does not exclude inventions for therapeutic or diagnostic purposes, which are applied to the human embryo and are useful to it.’ Such inventions, for example advances in assisted reproductive technologies, remain patentable (recital 42 of the Directive and par. 44–46 of the judgement).

Finally, the European Court ruled that derivative processes or technologies cannot be patented if their invention required prior destruction of a human embryo. It is irrelevant that the destruction of the embryo occurred at a stage long before the

The European Court's broad definition of the concept of human embryo has received considerable criticism both from scientists and from legal experts alike. The European Court declares that an autonomous and uniform definition of human embryo in EU law aims to maintain fairness in the internal market, and exceptions to the Biotech Directive would leave national laws no room for discretion. However, the Lisbon Treaty framework, established well before the *Brüstle* case, explicitly provides the European Court the possibility to adopt a more flexible approach, (e.g., Article 4(2) TEU) taking into account different attitudes in the Member States towards stem cell research. This was also demonstrated in *Netherlands v European Parliament and Council*, where the European Court ruled in 2001 that EU Member States have discretion in interpreting the Biotechnology Directive in light of their own social and cultural differences (de Vries, 2013). Unfortunately, in the *Brüstle* case, the European Court appeared to waive this flexibility.

So what considerations may have spurred the European Court's decision? We speculate that, with respect to the *Brüstle* case, the European Court's strong commitment to the EU single market and *principle of supremacy* (EU law takes precedence over national law) discouraged a more flexible approach.

Second, the European Court's perspective may have been influenced by increasing the importance of fundamental rights in EU law; in particular, the right to property and the right to life. However, the Strasbourg Court on Human Rights, which supervises the European Convention on Human Rights (ECHR), allows Member States considerable flexibility in determining, for instance, when life begins and who is a person (Plomer, 2012, p. 127). Herein lies potential conflict between the European and Strasbourg Courts since the adoption of the Lisbon Treaty mandates that the European Union must accede to the Convention (Article 6, Treaties of the EU).

Finally, the general principle of proportionality (Article 52(1), EU Charter) states that given several appropriate measures, the least severe option must be adopted.

It is therefore argued that EU legislature and the European Court are disproportionately restricting patent rights, by defining the concept of human embryo so inclusively and hence, excluding patentability of all types of stem cell research (Plomer, 2012).

creation or implementation of the invention, as in the *Brüstle* case, where neural stem cells were produced from an established ES cell line (par. 49 of the judgement).

The final outcome

The *Brüstle* judgement was referred back to the German Federal Court, which partially upheld the patent. The court pronounced *Brüstle*'s patent invalid to the extent that it made use of stem cell lines derived from human embryos. However, the application was found valid with respect to the process of generating neural cells from ES cells on the condition that *Brüstle* amend his claims to state that they do not, *per se*, require the destruction of human embryos. The German Federal Court considers the derivation techniques protected under the general international patent formulation, which enables 'a person skilled in the art' to produce *Brüstle*'s claim (par. 27–33 of the judgement); therefore, the patent does not need to specify them.

The German Federal Court also reasoned that stem cells, on their own, are incapable of commencing life, referring to two articles regarding the derivation of ES cells from non-viable human blastocysts (par. 34 of the judgement). In these articles, Gavrilov *et al* (2009, 2011) describe the derivation of human ES cell lines from irreversibly arrested blastocyst embryos. While certain cells within these embryos are still

alive and can yield ES cell lines, such embryos are functionally dead. Since irreversibly arrested embryos cannot resume development, the German Federal Court argues that the definition of an embryo as 'an entity that can commence the process of human development' does not apply to such blastocyst embryos.

Overall, there is general concern among researchers in light of the European Court's confusing judgements: how can EU Member States standardize patentability, if the European Court dictates that a human embryo be broadly defined, yet leaves it up to individual nations to qualify this definition at the blastocyst stage—the stage commonly used for the derivation of ES cells?

Impact on stem cell research in Europe: comparisons with the USA and Asia

It is important to note that the European Court's judgement only covers patent law. However, the ruling does not cover stem cell research as such irrespective of a patent claim, and the authorization of stem cell-based medicines, which are subject to specific legal regimes in the EU Member States. Nevertheless, the *Brüstle* ruling has significant drawbacks for the commercial exploitation of stem cell inventions in the pharmaceutical industry. In practice, the inventor will transfer the right to commercially exploit the new technology by assignment or licensing. Without such an exclusive right, the production of new medicines would be an economic risk that pharmaceutical industries may not be inclined to take.

Fewer European patents on stem cell-based inventions reduce Europe's competitive position against other economies such as the USA and Asia, where morality exclusions on patents do not exist or are more liberally applied. For example, Japan also has a morality exclusion on patents: an 'invention that is liable to injure public order, morality or public health shall not be patented'. Yet, an inventory made by the Hinxton group shows that Japan does not strictly adhere to the exclusion when it comes to patenting human ESC-related inventions. Therefore, Europe appears to stand alone in its strict application of this exclusion to human ES cells.

In the USA, the Supreme Court ruled in *Diamond v Chakrabarty* that 'anything under the sun made by men' is patentable regarding a patent claim for a man-made bacterium capable of breaking down crude oil. Instead of restricting patentability, the USA addresses the morality of stem cell use by strict legislation on public funding. This more liberal approach may drive researchers to seek patents in the USA. This may not affect academic research in Europe directly, since the goal of academic research is to provide discoveries, not patents. Yet, the restrictions on stem cell patents in Europe may be an impetus for the pharmaceutical industry to prefer collaborations with academic partners in the USA, where the results of the work are better protected.

Are iPSCs at risk of non-patentability?

The European Court's broad definition of a human embryo may unintentionally put novel technologies such as iPSCs at risk of non-patentability as well (Spranger, 2012). iPSCs are functionally indistinguishable from human ESCs, but do not

carry the same moral burden since they are derived from somatic cells of consenting donors rather than from pre-implantation embryos. Technically, however, all pluripotent stem cells may be 'capable of developing into a human being', and, as such, it is unclear whether iPSCs would fall under the same non-patentability restrictions as hESCs. For example, it is well known that murine iPSCs are capable of tetraploid complementation, a technique that allows the formation of a mouse that is entirely stem cell-derived. While the ability of human iPSCs to form an embryo cannot be tested for ethical reasons, *in vitro* experiments have demonstrated that these cells are capable of forming every cell type in our body. If one assumes that human and murine iPSCs are functionally similar, then it could be possible to derive a human embryo from a human iPSC line, and therefore argue that these cells are not patentable. It would therefore make sense to refine the European Court's judgement and dissociate theoretical intrinsic properties of stem cells from their actual use in the invention for which patent protection is sought.

At the national level, Member States appear to be more forward thinking with respect to novel approaches that alleviate the moral and societal concerns about using pluripotent cells for research. Since the European Court deferred judgement to the national courts to decide at what embryonic stage cells should be regarded as human embryo (Paton and Denoon, 2011, p 594; Harmon *et al*, 2013, p 94), they have considerable freedom to allow hESC-based patents. The German Federal Court already ruled that ES cell lines as such do not fall under the concept of a human embryo. Additionally, the UK Intellectual Property Office (IPO)

specifically excludes iPS cells from the definition of a human embryo. In fact, the IPO changed its guidelines on the patentability of human ES cells after the Brüstle judgement and the new guidelines state: '*Induced pluripotent cells which are obtained from the de-differentiation of an adult cell by the forced expression of certain genes are clearly not obtained from human embryos and cannot go on to form a human being. Therefore, these cells are not subjected to the exclusions of Par. 3(a) or Par. 3(d) of Schedule A2.*' [The referenced schedule contains the morality exclusions, which correspond to Article 6(2)(c) of the Biotechnology Directive].

Germ cells and embryos from iPSCs

It seems therefore that, for now, iPSCs and their derivative technologies are patentable. However, as research progresses, the lines between embryo and stem cell line are increasingly blurred.

In 2011, the laboratory of Mitinori Saitou reported the generation of germ cell precursors *in vitro* from murine ESCs (Hayashi *et al*, 2011). When transplanted into the testes of infertile mice, these germline stem cells gave rise to functional sperm. Even though the procedure involved an obligatory *in vivo* step to complete the differentiation, it does provide a direct developmental path from pluripotent stem cell to sperm. A year later, the same laboratory demonstrated the *in vitro* development of oocytes from murine ESCs and iPSCs, which, upon fertilization, could give rise to viable offspring (Hayashi *et al*, 2012). Since it is now possible to generate both male and female gametes from pluripotent

Figure 1 Schematic depiction of the patentability of human pluripotent stem cells. The European court decided that human embryonic stem cells as well as their derivatives are not patentable, regardless whether the embryo from which these cells are derived was the result of a fertilization event (middle left) or created 'artificially', as is the case for example in androgenetic embryos (top left) generated through injection of one or two sperm into an enucleated oocyte, or parthenogenetic embryos (bottom left) that result from activation of an unfertilized oocyte. However, the European Court left it up to National courts to decide whether the blastocyst stage of development constitutes a human embryo, creating uncertainty about the status of these cells and derivatives (middle grey-shaded area). Inventions arising from human somatic cells are patentable (Right, green-shaded area), but somatic-cell derived induced pluripotent stem cells enter a grey zone. Recently, the Saitou laboratory demonstrated the derivation of both Eggs and sperm from iPSCs, indicating that a direct developmental path exists from iPSCs to new embryos via this gamete intermediate. iPSC-derived oocytes can generate parthenogenetic embryos in the absence of fertilization or be fertilized with iPSC-derived sperm to generate a new embryo.

stem cells, iPSC line(s) could give rise to both sperm and oocyte, and, when combined, generate a viable embryo (Figure 1). From a legal perspective, this demonstrates that iPSCs are capable of commencing the development of an embryo and as such would fall under the non-patentability restrictions.

It is not inconceivable that, in the coming years, new technologies will allow the development of human gametes from pluripotent stem cells. Indeed, several laboratories have already demonstrated the derivation of human primordial germ cells from human pluripotent stem cells (Clark *et al*, 2004). A recent paper from Nakaki *et al* (2013) describes a cocktail of transcription factors that may make the process of *in vitro* germ cell differentiation more efficient. Factor-induced germ cells are efficiently generated from murine pluripotent stem cells and are capable of engrafting into the seminiferous tubules after testicular transplantation and differentiating into functional sperm. Further development of such technologies could enable the generation of both oocyte and sperm from human iPSC lines. In fact, the creation of an oocyte from human iPSCs would be sufficient to establish a direct developmental path between a pluripotent stem cell and a parthenogenetic embryo.

Resolving the uncertainty

Recently, a new case has been referred to the European Court by the High Court of England and Wales (Chancery Division,

Patents Court), which concerns two patent applications submitted by the International Stem Cell Corporation (ISCC), entitled 'Parthenogenetic activation of oocytes for the production of human embryonic stem cells' and 'Synthetic cornea from retinal stem cells'. The central question revolves again around the interpretation of 'capable of commencing the process of development of a human being.' The European Court will have the chance to (partly) reconsider, or at least refine its judgement in the Brüstle case. It would be more prudent to support a more pluralistic and ethical rather than technical and purely legal approach to the patentability of stem cell research. In support of such refinement, the European Commission recently announced that it has decided to set up an expert group to examine the implications of patent law in the field of biotechnology and genetic engineering, and to provide legal and technical expertise, which will help the Commission with its reporting obligations under the Biotechnology Directive. This could perhaps be a starting point in revising the current legal framework.

Acknowledgements

We thank Sarah Opitz and Holger Breithaupt for critical reading and help with editing of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

References

- Bonadio E (2012) Biotech patents and morality after Brüstle. *Eur Intellect Property Rev* **34**: 433–443
- Burke S (2012) Interpretive clarification of the concept of "human embryo" in the context of the Biotechnology Directive and the implications for patentability: Brüstle v Greenpeace eV (C-34/10). *Eur Intellect Property Rev* **34**: 346–350
- Clark AT, Bodnar MS, Fox M, Rodriguez RT, Abeyta MJ, Firpo MT, Pera RAR (2004) Spontaneous differentiation of germ cells from human embryonic stem cells in vitro. *Hum Mol Genet* **13**: 727–739
- Cyranoski D (2013) Stem cells cruise to clinic. *Nature* **494**: 413
- Daley GQ (2012) The promise and perils of stem cell therapeutics. *Cell Stem Cell* **10**: 740–749
- de Vries S (2013) The protection of fundamental rights within Europe's Internal Market after Lisbon—an endeavour for more harmony. In: de Vries S, Bernitz U, Weatherill S (eds) *The Protection of Fundamental Rights in the EU after Lisbon*. Oxford: Hart Publishing, pp 59–94
- Evans MJ, Kaufman MH (1981) Establishment in culture of pluripotential cells from mouse embryos. *Nature* **292**: 154–156
- Gavrilov S, Marolt D, Douglas NC, Prosser RW, Khalid I, Sauer MV, Landry DW, Vunjak-Novakovic G, Papaioannou VE (2011) Derivation of two new human embryonic stem cell lines from nonviable human embryos. *Stem Cells Int* **2011**: 765378
- Gavrilov S, Prosser RW, Khalid I, MacDonald J, Sauer MV, Landry DW, Papaioannou VE (2009) Non-viable human embryos as a source of viable cells for embryonic stem cell derivation. *Reprod Biomed Online* **18**: 301–308
- Harmon SHE, Laurie G, Courtney A (2013) Dignity, plurality and patentability: the unfinished story of Brüstle v Greenpeace. *Eur Law Rev* **38**: 92–106
- Hayashi K, Ogushi S, Kurimoto K, Shimamoto S, Ohta H, Saitou M (2012) Offspring from oocytes derived from in vitro primordial germ cell-like cells in mice. *Science* **338**: 971–975
- Hayashi K, Ohta H, Kurimoto K, Aramaki S, Saitou M (2011) Reconstitution of the mouse germ cell specification pathway in culture by pluripotent stem cells. *Cell* **146**: 519–532
- Hyun I, Lindvall O, Ahrlund-Richter L, Cattaneo E, Cavazzana-Calvo M, Cossu G, De Luca M, Fox JJ, Gerstle C, Goldstein RA, Hermerén G, High KA, Kim HO, Lee HP, Levy-Lahad E, Li L, Lo B, Marshak DR, McNab A, Munsie M *et al* (2008) New ISSCR guidelines underscore major principles for responsible translational stem cell research. *Cell Stem Cell* **3**: 607–609
- Martin GR (1981) Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci USA* **78**: 7634–7638
- Nakaki F, Hayashi K, Ohta H, Kurimoto K, Yabuta Y, Saitou M (2013) Induction of mouse germ-cell fate by transcription factors in vitro. *Nature* **501**: 222–226
- Paton M, Denoon A (2011) The ramifications of the Advocate General's Opinion in the Oliver Brüstle case. *Eur Intellect Property Rev* **33**: 590–596
- Plomer A (2012) After Brüstle: EU accession to the ECHR and the future of European patent law. *Queen Mary J Intellect Property* **2**: 110–135
- Spranger TM (2012) Case C-34/10, *Oliver Brüstle v. Greenpeace e.V.*, Judgment of the Court (Grand Chamber) of 18 October 2011, nyr. *Common Market Law Rev* **49**: 1197–1210
- Takahashi K, Okita K, Nakagawa M, Yamanaka S (2007a) Induction of pluripotent stem cells from fibroblast cultures. *Nat Protoc* **2**: 3081–3089
- Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S (2007b) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* **131**: 861–872
- Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**: 663–676
- Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic stem cell lines derived from human blastocysts. *Science* **282**: 1145–1147
- Varju M, Sándor J (2012) 'Patenting stem cells in Europe: the challenge of multiplicity in European Union law'. *Common Market Law Rev* **49**: 1007–1038