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Understanding the ethical concerns that have shaped European regulation of human embryonic stem cell research

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Received: 13.06.2012 *Accepted: 22.08.2012* *Published: 10.10.2012*

Abstract

Human embryonic stem cell research has generated much hope, but also fear and repulsion. National legislators, as well as the European Parliament, the European Patent Office and the European Court of Justice have had to make decisions relating to what is or is not allowed in the field of hESC research and patenting, and their decisions are often difficult to reconcile. In order to understand this divergence and the specific restrictions that different regulators impose, insight is needed into the different opinions regarding the moral status of the pre-implantation embryo (blastocyst), into the moral distinction between using IVF embryos donated for research versus creating embryos for research purposes, and into the moral distinction between producing and using hESC lines for non-commercial research and allowing such production and research in a commercial or industrial setting. While one need not agree that all of these perceived differences are in fact morally relevant, knowing that many people perceive them as being relevant is in itself valuable for understanding the debate and the decisions that different regulators make.

Keywords: *embryo research, ethics, legislation, stem cell research*

INTRODUCTION

Throughout Europe there is a great divergence of policies addressing human embryonic stem cell research (hESCR), reflecting the contrasting views that exist with regard to the ethical permissibility of using human embryos for research purposes. In this article, an overview is presented of the main ethical considerations that lie at the heart of different European policies.

REGULATION OF HUMAN EMBRYONIC STEM CELL RESEARCH IN EUROPE

Since the first hESC line was established in 1998, many European countries have enacted specific legislation to regulate stem cell research (1). One issue that all countries agree upon, is that reproductive cloning should not be pursued, however there is little agreement on any other aspect. The most *permissive* countries, namely Belgium, Spain, Sweden and the UK, allow research on existing hESC lines, hESC derivation and even somatic cell nuclear transfer (SCNT), but they have installed regulatory bodies and ethics committees to ensure oversight. *Moderate* countries, for example France and The Netherlands, allow hESC research and hESC derivation, but only from spare IVF embryos (that is, embryos that were created in the course of an IVF treatment, but that will not be transferred to the patient) that were donated for research. In the group of the most *restrictive* countries we find Germany and Italy, where SCNT and hESC derivation are forbidden, hESC research on imported stem cell lines is subjected to strict limitations and no public funding is available for this research. Ireland and Poland also forbid hESC derivation but have no specific legislation that either allows or forbids hESCR on imported hESC lines. Due to this great divergence, collaboration between researchers from different countries is fraught with numerous difficulties (2).

At the European level, article 18 of the Convention on Human Rights and Biomedicine of 1997 (also known as the Oviedo convention) states that "[w]here the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo" and "[t]he creation of human embryos for research purposes is prohibited" (3). A majority of European countries has signed this convention and numerous countries have also ratified it. The UK and Belgium have neither signed nor ratified the convention, as they allow embryo creation for research purposes under certain conditions. Another agreement that is important at the European level, is the agreement that was reached in 2006 – after much debate – to include hESCR as eligible for EU funding in the Seventh Framework programme for research and technological development. Researchers can apply for EU funding if their research involves the use of existing hESC lines and if it is not forbidden in the country where it will be performed. However, EU funds cannot be used for the derivation of hESC lines. This agreement on EU funding is remarkable, as it means that the countries on the restrictive side of

the spectrum contribute to the funding of research projects in foreign countries that are forbidden in their own territory.

WHERE IT ALL STARTS: THE MORAL STATUS OF THE HUMAN EMBRYO

How can we explain this wide variance in European policies? The main issue dividing European lawmakers and citizens alike, is what degree of moral status should be conferred upon the embryos used in the research (4-11). Embryonic stem cells are typically obtained by isolating and culturing the inner cell mass of a human blastocyst, which is a 5 day old embryo. By performing this isolation, the embryo is destroyed, which is ethically troubling for a large number of people. Three different lines of moral reasoning can be discerned in the debate.

First, one can take the principled, deontological stance that the destruction of human embryos represents such a great infraction of respect for human dignity that it is never justified, regardless of the benefits that it might lead to. This position is for example taken by the Roman Catholic Church, as a logical consequence of its teachings that ensoulment takes place at the time of conception and that therefore the killing of an embryo equals murder, even at a very early stage of development. This explains why countries such as Ireland and Poland, two nations where Catholicism is very widespread, are explicitly opposed to hESCR.

Second, at the other end of the spectrum we also find a principled position, namely, that human blastocysts have none of the properties (such as sentience or self-awareness) on the basis of which dignity or respect might be due to them. Therefore, embryo destruction is no greater infringement on human dignity than the destruction of human cells and it can certainly not be compared to the destruction of a person. If one adheres to this position, the destruction of embryos is a trivial matter which should be allowed even if the possible gains for humanity are small. While this is a stance that is certainly present in the European population and which is quite prominent in the philosophical literature on the subject, it is not adopted as such by any European country, as even the most permissive countries have specified minimum requirements for the scientific validity and relevance of the research for which embryos are used.

Third, between these two extremes is the position that while one cannot recognise the same status for embryos that one does for ‘full-grown’ human beings, the facts that they can grow into human beings and that they are generally cherished by their progenitors require us to treat them with a level of respect that is not absolute, but not trivial either. This stance leads to a utilitarian balancing between the benefits of the research for which embryos are destroyed and the disadvantage of embryo destruction itself. If the benefits outweigh the disadvantage, then embryo research is ethically justified.

Almost all European legislations reflect this compromise position. However, there is little uniformity between the different policies as the balancing act is highly dependent on the moral status that is recognised for the blastocyst. Whereas the first two (extreme) positions we discussed represent a very clear opinion about the moral status of the embryo (either absolute or absent), within this third position we find a wide spectrum of opinions about the degree of respect that blastocysts should be treated with. As it is most unlikely that all European countries will ever reach a mutual standpoint on the issue of the moral status of the embryo, the European Union considers ethical standpoints to be the authority of the Member States.

SPARE IVF EMBRYOS DONATED FOR RESEARCH VERSUS EMBRYOS CREATED FOR RESEARCH

Besides the different views on the moral status of blastocysts, there are also other factors at play in shaping stem cell policies. As a general pattern, there is for example a much lower degree of acceptance for the creation of embryos specifically for research purposes than for the use of embryos that were created in the course of an IVF treatment, but that are 'left over' when patients decide to forego further treatment. It is remarkable that this distinction is at play not only in the intermediate countries' legislations, but also in both the more restrictive and the more permissive legislations. For example, the Oviedo convention (intermediate) allows stem cell derivation from IVF embryos donated for research, but not from embryos created for research purposes, Germany (restrictive) allows the importation of stem cell lines that were derived from IVF embryos donated for research under certain conditions, but not of those derived from embryos created for research, and Belgium (permissive) only allows the creation of embryos for research purposes if the research goals cannot be obtained with spare IVF embryos.

This begs the question as to what the morally relevant differences are between destroying an IVF embryo donated for research and destroying an embryo created for research (4, 12-15). Merely referring to the balancing act between the moral status of the embryo and the benefits of the research is not sufficient here, as there is no reason why embryos created for research would have a higher moral status than spare IVF embryos. On the contrary, IVF embryos tend to be very valuable to the patients for whom they were created. However, there are other factors at play. An ethical distinction between using donated IVF embryos versus embryos created for research can for example be based on the 'doomed embryo rule' (16) or the 'nothing is lost principle' (17). As the spare IVF embryos are already doomed to be destroyed, whether or not they are used for research purposes does not change the number of embryos that are being destroyed. Only the method of destruction changes and there is no reason to regard one method as worse than the other. The use of spare IVF embryos donated for research therefore does not increase the

disadvantages, but it does increase the benefits, so that the utilitarian calculus is better when they are used in research than when they are left to perish. This means that in the case of spare IVF embryos, there is even a moral imperative to use them rather than to simply discard them (18). This is not the case when embryos are being created explicitly for research purposes, as in that case, the disadvantages increase due to an additional number of embryos being 'sacrificed'.

The doomed embryo rule is intuitively very persuasive, but this argument neglects the fact that the embryos are not doomed by an uncontrollable twist of fate, but rather by how IVF treatments are routinely performed, namely by overstimulating the ovaries and fertilising more oocytes than are needed. The existence of spare embryos can be avoided by fertilising only one or two oocytes per cycle and transferring all the embryos instead of cryopreserving some of them. Italy, for example, implemented a rule that all created embryos should be immediately transferred to avoid the existence of spare embryos.

The only way, then, that the doomed embryo rule can still be applied, is if one starts from the premise that the creation and destruction of embryos during IVF treatment is morally justified, but not in hESCR. There are two possible arguments to support this stance, a consequentialist one and a deontological one. First, one might argue that the benefits of IVF treatment are greater than those of hESCR (so that the utilitarian calculus is positive for the former, but negative for the latter). If and when hESCR delivers on its promise to revolutionize regenerative medicine, this argument may become hard to maintain, but at present, it is a defensible stance (although even in this experimental phase, not all would agree that hESCR is an undertaking inferior to infertility treatment). Second, one could refer to the difference in intention at the time of embryo creation and the doctrine of double effect. In IVF treatment, the doctors who create an embryo do not have the intention to destroy it afterwards, but to transfer it to an IVF patient. Only in those cases where the patient later decides that she does not want her embryos to be transferred to her womb (or that of another woman), embryo destruction becomes part of the enterprise of infertility treatment, but merely as a side-effect of the original, intended goal, which is reproduction. However, in hESCR, the researchers who create an embryo *do* have the intention to destroy it (from the onset), as the goal they pursue – stem cell derivation – *requires* the prior destruction of that embryo. It is therefore not a side-effect, but a crucial step and as such it cannot be said to be unintended. In other words, while IVF embryos are created with the possibility of 'self realisation' in mind, research embryos are reduced to instruments of science. Based on this distinction, people may approve the creation of embryos for IVF, but not for research purposes. Once the embryos are created and it turns out that they will eventually not be transferred, opponents of the creation of embryos for research may still approve the use of IVF

embryos donated for research based on the 'nothing is lost' principle.

This second argument has two weaknesses. The first one is that although those who create embryos for IVF treatment do not intend to destroy them, they can foresee that a certain percentage of them will eventually be destroyed so that they cannot be completely 'absolved' from responsibility in this matter. A second one is that although the intent to destroy the IVF embryo may be absent at the time of creation, it is not absent at the time when they are used for hESCR. In other words, although the fertility specialist may not intend to destroy the embryo, the stem cell researcher does.

As a counter argument, supporters of the use of IVF embryos donated for research but not of embryo creation for research might refer to the concept of complicity and the separation principle. The separation principle was first introduced in the context of research on aborted foetuses and it requires that the decision to abort precedes the decision to use the foetal tissue in research. This way, the researcher who uses the foetal tissue cannot be judged to be an accomplice to the alleged moral wrong of abortion, although he or she indirectly benefits from it. In the distinction between using donated IVF embryos rather than creating embryos for research, the same idea can be invoked. When embryos are specifically created for research purposes, the researchers decide that these embryos will be destroyed and can therefore be held morally accountable. When donated IVF embryos are used, the researcher had no impact on the decision not to transfer these embryos to the womb and can thus not be morally accountable for the decision that they are to be destroyed. However, is this argument convincing? Building further on the analogy with the use of foetal tissue, it is not difficult to see that there is a crucial difference between a researcher using foetal tissue after an abortion and one removing the inner cell mass of a blastocyst. The blastocyst is destroyed during and because of the manipulations carried out by the researcher, while the foetus is no longer alive when the researcher performs his/her research on the tissue. Therefore, whereas the separation between the researcher and the killing of the foetus is complete, that between the researcher and the killing of the embryo is not.

In short, we can conclude that there are differences between using donated IVF embryos versus creating embryos for hESCR in terms of consequences, intent and/or complicity, which are deemed morally relevant by some people. At the same time, based on the counterarguments that were presented, one can also adopt the stance that these differences are *not* morally relevant (12-13). In any case, the creation of embryos for research purposes is seen by some countries (such as The Netherlands) as 'crossing the line' into an absolute wrong that is forbidden under every circumstance and by others (such as Belgium) as a wrong that requires more justification than the destruction of an IVF embryo donated for research.

DERIVING STEM CELL LINES VERSUS USING EXISTING STEM CELL LINES

Besides the distinction between the use of IVF embryos donated for research and the creation of embryos for stem cell derivation, another distinction that is deemed morally relevant by several countries and which is also embedded in the Seventh Framework programme, is that between the derivation of new hESC lines and the use of existing hESC lines. As mentioned above, EU funding is granted for hESC research, but not for hESC derivation, and Germany allows research on imported hESC lines (if derived from spare embryos before May 1st 2007), but does not allow derivation in its territory. Again, the basis for this distinction is the concept of complicity.

Various theories have been proposed regarding moral complicity. Some regard causation as a necessary condition (either only direct causation or also indirect causation), while others also include benefiting from evil or tolerating evil as sufficient conditions (14, 19-21). By not allowing stem cell derivation, but nevertheless allowing research on imported hESC lines, countries can escape responsibility by direct causation (a researcher using an existing stem cell line cannot be said to have killed the embryo from which the line was derived) and again rely on the argument that the utilitarian calculus will be better if existing stem cell lines are put to a good use, than when they are not (which is the same reasoning that can be applied to defend the use of spare IVF embryos donated for research).

However, one can also reject the idea that researchers using existing stem cell lines are not responsible for the destruction of embryos. Even if one is willing to accept that it is theoretically possible to benefit from an act that is perceived as wrong without becoming an accomplice to the wrong (21), the chain of complicity is difficult to break completely in the context of hESCR (22, 23). This is due to a combination of two factors: the variety of regulations throughout the world and the fact that the (alleged) wrong is not completely in the past, but is part of an ongoing field of research. If *all* countries would decide that only research on existing stem cell lines was allowed but that no new lines could be created (so that the destruction of embryos for research purposes was completely in the past), one might say that those researchers who never derived a stem cell line themselves cannot be held accountable for embryo destruction (although not everyone would agree (14)). However, given the fact that embryo destruction is ongoing in more permissive countries, one might imagine researchers from those countries 'catering' to researchers in less permissive countries by producing the particular stem cell lines that are needed. To avoid this, Germany only allows research on stem cell lines that were derived before a cut-off date, which is currently May 1st 2007. However, the effectiveness of this cut-off date is undermined by the fact that it is not eternally fixed (22, 24). In fact, Germany

originally set the cut-off date as January 1st 2002, but later moved it as more recent cell lines proved to be of better quality. The quality of hESC lines will continue to improve and, especially when the research moves towards clinical trials, new lines that are free from animal-derived products will be needed. Thus, it can already be foreseen that the cut-off date will be moved again in the future. Moreover, even if researchers from permissive countries are not literally catering to those in restrictive countries, it is quite likely that findings from research on existing hESC lines will lead to new research in more permissive countries and thus lead to more embryo destruction.

In short, while a country can limit the extent of its complicity by allowing importation of hESC lines, but not derivation, some kind of 'residual complicity' is inescapable. For those who consider moral complicity to be a black-or-white concept (either one is responsible for a harm, or one is not), the distinction between stem cell derivation and research on existing lines will therefore be insufficient to render the former unacceptable and the latter acceptable. However, for those who consider moral complicity to be a gradual concept so that the responsibility of researchers using existing hESC lines is outweighed by the benefits of the research, while the responsibility of those who derive the hESC lines is not, the distinction *will* be morally relevant.

ALLOWING RESEARCH VERSUS ALLOWING PATENTS

A final morally relevant distinction that is made at the European level, is that between performing hESCR, which is allowed and funded (each under specific circumstances, see above) on the one hand and patenting the results of this research on the other hand, which is not allowed. The European Parliament passed a resolution in 2005 which "insists that the creation of human embryonic stem cells implies the destruction of human embryos and that therefore the patenting of procedures involving human embryonic stem cells or cells that are grown from human embryonic stem cells is a violation of Article 6(2)(c) of the Directive" (25). The Article referred to states that "inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; […] the following, in particular, shall be considered unpatentable: […] uses of human embryos for industrial or commercial purposes" (26).

There are two important cases regarding the patentability of hESCR. The first one has become known as the WARF-case and was decided by the Enlarged Board of Appeal of the European Patent Office in 2008 (27). The second one is Brüstle vs Greenpeace and was decided by the European Court of Justice (ECJ) in 2011 (28).

The WARF-case refers to a patent

application for compositions containing hESCs that was filed by the Wisconsin Alumni Research Foundation in 1996 and that was denied based on rule 28(c) of the European Patent Convention, which states that European patents are not granted in respect of biotechnological inventions which concern uses of human embryos for industrial or commercial purposes. In its ruling the Enlarged Board of Appeal made it clear that whether or not the embryo destruction is itself part of the invention as defined in the patent application is irrelevant if, at the date of filing of the application, the products claimed in the application "could be prepared exclusively by a method which necessarily involved the destruction of the human embryos from which the said products are derived" (27). However, as argued by Sterckx and Cockbain (29), the ruling left a "deposit loophole", meaning that patentability could be acknowledged if a hESC line was deposited in a stem cell bank prior to the patent application being filed so that it could be used as a 'source material' allowing future attempts to perform the invention to be carried out without further embryo destruction.

This deposit loophole was closed in the Brüstle vs Greenpeace case. In this case, Greenpeace sought the annulment of a German patent that was held by Olivier Brüstle, relating to neural precursor cells derived from hESCs. The German *Bundesgerichtshof* asked the European Court of Justice for a clarification of Article 6(2)(c) of Directive 98/44/EC on the legal protection of biotechnological inventions. In this case, clarification was sought on three questions: (1) What is meant by the term "human embryos" in Article 6(2)(c)? (2) What is meant by the expression "uses of human embryos for industrial or commercial purposes" in the same article? (3) Is technical teaching to be considered unpatentable pursuant to Article 6(2)(c) of the Directive even if the use of human embryos does not form part of the technical teaching claimed within the patent, but is a necessary precondition for the application of that teaching?

Following the opinion of advocate general Yves Bot, the ECJ ruled that (1) entities arising from either the fertilisation of a human oocyte or from somatic cell nuclear transfer, as well as parthenotes, are to be considered as embryos; (2) the exclusion from patentability concerning the use of embryos for industrial or commercial purposes covers the use of human embryos for purposes of scientific research; (3) inventions are excluded from patentability where the technical teaching which is the subject-matter of the patent application requires the prior destruction of human embryos or their use as base material.

This ruling was ill received by most stem cell scientists and their supporters (30). Although the court insists that it did not make any moral judgement on hESCR as such, but only applied the existing EU Directive, its specific interpretations in answering all three questions are rather on the restrictive side of the spectrum than on the permissive one. Regarding the definition of the embryo, the fact that parthenotes are included, for example, is not an obvious choice, as parthenotes lack

paternal imprinting and are therefore inherently incapable of completing embryogenesis. Although they carry human DNA and originate from reproductive tissue (an oocyte), they are an early stage of ovarian teratomas, not of humans.

The answer to the second question is equally un-obvious. The ruling was based on the idea that a patent application is by definition in the realm of commerce or industry and that the research leading to the subject of the patent application must be deemed to have taken place in the commercial or industrial context, *irrespective* of the context in which it actually took place.

The answer to the third question is probably the most controversial as it explicitly goes further than the WARF case (by closing the deposit loophole), and – if consistently applied – may have far reaching consequences even beyond the field of hESCR. By not only excluding the commercial or industrial use of embryos as such from patentability, but instead extending this exclusion to every invention that was based on earlier embryo destructive research, a whole range of inventions in the field of medically assisted reproduction and ironically also the entire field of iPS cell research are excluded, as this field of research relies heavily on findings from hESCR. The court could have avoided this implication by specifying that inventions are excluded from patentability only when there is a *material* link between the destroyed embryo and the performance of the invention, and not when there is only an *informational* link. However, as it is stated now, it is extremely restrictive.

How far reaching the implications of the case at hand will be, remains to be seen. First, the verdict only applies to European patent applications, so researchers can still file patent applications in, for example, the US or Asia. Second, although the decision in the Brüstle vs Greenpeace case is interpreted by many as a conviction of hESCR, it neither prohibits the research or the commercial exploitation of its results, nor the patenting of 'side products' such as culture media. Also, in theory, the absence of patents in this field can have both a limiting and a liberating effect. On the one hand, less funding from European private companies and even from public funding institutions (as the 'valorisation' aspect of a funding application is increasingly important) is to be expected. On the other hand, researchers are no longer restricted by patents that are held by their competitors and that are now considered to be invalid. At present, it is therefore unpredictable what the overall ramifications of these rulings in patent law will be for hESCR.

CONCLUSION

Since the first derivation of human embryonic stem cells in 1998, this research field has instilled hope, but also fear and repulsion. National legislators, as well as the European Parliament, the European Patent Office and the European Court of Justice have had to make decisions relating to what is or is not allowed in the field of hESC research and patenting, and their

decisions are often difficult to reconcile. This means that Europe has become a patchwork of very permissive, very restrictive and intermediate positions. In order to understand this divergence and the specific restrictions that different regulators impose, insight is needed into the different opinions regarding the moral status of the pre-implantation embryo (blastocyst), into the moral distinction between using IVF embryos that are donated for research versus creating embryos for research, and into the moral distinction between producing hESC lines and using them for non-commercial research and allowing such production and research in a commercial or industrial setting. While one need not agree that all of these perceived differences are in fact morally relevant, knowing that many people perceive them as being relevant is in itself valuable for understanding the debate and the decisions that different regulators make.

ACKNOWLEDGEMENTS

I would like to thank professor Guido Pennings, Julian Cockbain and professor Sigrid Sterckx for their helpful comments on this manuscript.

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