The trouble with embryos

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In an effort to quell ongoing debate about the ethics of human embryonic stem cell (hESC) research, there have been concerted efforts to develop ethical standards for both embryo and hESC research and to entrench these standards in law. Surprisingly these efforts have not included efforts at standardizing the meaning of the pivotal term 'embryo'. This paper reviews the legal framework for embryo research in the United Kingdom, the United States and Germany and highlights the absence of any agreed upon standard for what counts as a human embryo. This is an important lacuna, especially in light of the most recent advances in stem cell research involving the reprogramming of human somatic cell nuclei to generate human induced pluripotent stem (iPS) cells.

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From the time that James Thomson and colleagues (1998) first announced the successful derivation of human embryonic stem cell (hESC) lines, there has been a heated debate about the ethical acceptability of hESC research because this research entails the destruction of human embryos (see Prainsack et al., 2008a). In an effort to quell this debate, governments, quasi-governmental organizations, and professional organizations around the world have sought to develop ethical standards for embryo research and hESC research, and to entrench these standards in laws or research guidelines.

Together, these many and varied ethical and legal standards for embryo research and hESC research currently shape the field of stem cell science. Their importance can be measured by the fact that scientists consider these standards when making personal and professional choices about what kind of research to pursue and where, just as private and public funding organizations consider these standards when making decisions about where to invest their research dollars. As well, national research licensing committees, and national, regional, and local research review committees rely on these standards when deciding whether to authorize specific research proposals.

In the abstract this all seems very reasonable, but for the fact that we have erected an edifice of ethical and legal standards for hESC research, without prior agreement on what is and what is not a human embryo. Indeed, though debates about the moral status of the human embryo abound '(as do commentaries on the political culture of these debates (Jasanoff, 2005; Prainsack

et al., 2008b))', the pivotal question "What is a human embryo?" remains relatively under-explored.[1] As Sarah Franklin writes:

> The anxious attention so often directed at 'the' embryo, as in the perennial debate over 'the moral status of the human embryo', forgets that human embryos are now a vast and diverse population, imaged, imagined and archived in media as diverse as liquid nitrogen, DVDs, virtual libraries, t-shirts, logos and brandnames. Never very precise, the term 'embryo' is ever more a basket category, describing everything from a conceptus, a zygote or a blastocyst to a reconstructed cell, a fertilized egg or an embryoid body. (Franklin, 2006: 168)

Beyond this, Beatrix Rubin reminds us that the "national laws framing hESC research harbour divergent categorizations of the human embryo [and this] continues to perturb its appropriation as an experimental object of hESC research" (Rubin, 2008: 25).

The multiple social, cultural, political, ethical and legal understandings and categorizations of the human embryo is a serious problem for hESC research–a problem recently brought into sharp focus with the work of Shinya Yamanaka and colleagues (Takahashi et al., 2007) and James Thomson and colleagues (Yu et al., 2007) involving the successful reprogramming of human somatic nuclei to generate induced pluripotent stem (iPS) cell lines. Indeed, confusion about what counts as a human embryo explains why some enthusiastically celebrate this research, while others insist that such enthusiasm is misplaced. According to some, iPS cell research is ethically preferable to hESC research because it does not involve the destruction of human embryos. According to others, iPS cell research likely results in the creation of a new kind of human embryo and, as such, this research is no more or less ethically acceptable than hESC research. As suggested above, at the heart of the matter is confusion about what is and what is not a human embryo.

In this paper, we briefly review select legislative attempts made during the past twenty years to resolve the ethical debate concerning human embryo research (and more specifically hESC research), paying particular attention to the ways in which the human embryo is defined in legislation. For illustrative purposes, we look at the legal rules in the United Kingdom, the United States and Germany. We recognize that legal standards are distinct from (and may not reflect) ethical standards and we also recognize that there may be a wide and complex spectrum of ethical standards in any one jurisdiction regardless of what the law stipulates.

Against this backdrop, we then carefully consider the recent successful research to generate iPS cell lines. We leave to science the task of establishing the differentiation potential of iPS cells and resolving any debate surrounding the scientific claim that human iPS cells are comparable to hESCs (i.e., they satisfy the characterization standards developed for hESC lines). Instead, we focus our attention on the claim that iPS cells may be functionally and morally equivalent to human embryos, in which case they may just be a new kind of human embryo. The paper ends with a brief discussion of what is (or might be) a human embryo from an ethical perspective, when the term functions as a placeholder for 'protectable' human life.

Legal standards for human embryos, human embryo research, and hESC research

While there are many facets to the ethical debate about hESC research, for many, the central issue is the moral status of the developing human embryo. On the one hand, there are proponents of hESC research who insist that the human embryo is morally equivalent to other somatic cells and, as such, it need not be afforded any special protections. From their vantage point, research to derive hESCs that results in the destruction of the human embryo is ethically acceptable. On the other hand, there are opponents of hESC research who insist that "from the beginning" the human embryo has full moral status, and it ought not to be destroyed for the purpose of deriving hESCs. On their view, research to derive hESCs that results in the destruction of the human embryo is ethically unacceptable.

These competing ethical views, which represent different ends of a spectrum, typically find a more nuanced expression in legislation. For example, while jurisdictions that permit research to derive hESCs do not accept the claim that human embryos have full moral status, they also do not accept the claim that human embryos are morally equivalent to somatic cells. Indeed, most jurisdictions that permit research to derive hESCs allow that human embryos have some moral status (by virtue of their potential to become human persons) and are deserving of special respect (because they represent the beginnings of human life) (Anonymous, 1994). For these reasons, jurisdictions that permit hESC research stipulate clear limits on the nature, scope and duration of legally permissible embryo research.

Below, we briefly review the relevant legislation in three jurisdictions, each with a different approach to the regulation of human embryo research and a different perspective on the permissibility of such research. We look at the United Kingdom (a highly regulated, very permissive jurisdiction), the United States (generally an unregulated, very permissive jurisdiction as concerns privately-funded embryo research and, at the same time, a regulated, permissive jurisdiction as concerns publicly-funded embryo research), and Germany (a much regulated, very restrictive jurisdiction). In each instance we highlight the different legal and policy understandings of what constitutes a human embryo deserving of legal protections. In this way we set the stage for a discussion of whether iPS cells qualify as human embryos.

The United Kingdom

In the United Kingdom, research involving human embryos is regulated by the Human Fertilisation and Embryology Authority (HFEA) pursuant to the *Human Fertilisation and Embryology Act 1990* as amended by the *Human Fertilisation and Embryology Act 2008* (hereafter *HFE Act 1990* and *HFE Act 2008* respectively).

The *HFE Act 1990* originally defined the human embryo with reference to fertilization:

> 1.—(l) In this Act, except where otherwise stated—
> (a) embryo means a live human embryo where fertilisation is complete, and
> (b) references to an embryo include an egg in the process of fertilisation,
>
> and, for this purpose, fertilisation is not complete until the appearance of a two cell zygote. (United Kingdom, 1990:1, 1)

As well, the *HFE Act 1990* made it legal to create human embryos for research, provided the research was "necessary or desirable" relative to a set number of research purposes (United Kingdom, 1990:Schedule 2, 3.(1a)).

As stipulated in the *HFE Act 1990*, legitimate research purposes originally were limited to research into the treatment of infertility, the causes of congenital diseases, the causes of miscarriages, techniques of contraception, and the development of pre-implantation genetic diagnosis, with the option of specifying additional research purposes in future regulations (United Kingdom, 1990:Schedule 2, 3(2)). Notably, the original legislation did not permit human embryo research for the purpose of regenerative medicine. In January 2001, with a view to enabling hESC research, the *Human Fertilisation and Embryology (Research Purposes) Regulations* was passed (United Kingdom, 2001b). These regulations permitted the use of human embryos in research for the further purposes of "increasing knowledge about the development of embryos; increasing knowledge about serious disease, or enabling any such knowledge to be applied in developing treatments for serious disease" (United Kingdom, 2001b:2.(2)). Also in 2001, the government passed the *Human Reproductive Cloning Act 2001* "to prohibit the placing in a woman of a human embryo which has been created otherwise than by fertilisation" (United Kingdom, 2001a:1 (1-2)). While the *Human Reproductive Cloning Act* (2001) clearly recognized that human embryos could be created by means other than fertilisation, no changes were made to the definition of human embryo in the *HFE Act 1990*.

In 2008, the *HFE Act 1990* was amended, as a result of which the *Human Fertilisation and Embryology (Research Purposes) Regulations* and the *Human Reproductive Cloning Act* officially ceased to have effect. Further, the *HFE Act 2008* expanded the list of legitimate research purposes, and amended the definition of an embryo so as to legally recognize that a human embryo could be created by means other than fertilization:

> 1(1)—In this Act (except in section 4A or in the term "human admixed embryo")—
> (a) embryo means a live human embryo and does not include a human admixed embryo (as defined by section 4A(6)), and
> (b) references to an embryo include an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo." (United Kingdom, 2008:1, 1)

The explanatory notes for this circular definition of an embryo, state that the *HFE Act 2008* applies to "all live human embryos regardless of the manner of their creation" and for this reason "the definition no longer assumes that an embryo can only be created by fertilization" (United Kingdom Parliamentary House of Commons, 2008:Point 24). In addition, the law allows that the definition of an embryo can (within limits) be amended by regulation:

> 1(6) If it appears to the Secretary of State necessary or desirable to do so in the light of developments in science or medicine, regulations may provide that in this Act (except in section 4A) "embryo", "eggs", "sperm" or "gametes" includes things specified in the regulations which would not otherwise fall within the definition. (United Kingdom, 2008:1, 6)

A more expansive and less specific legal definition of an embryo is hard to imagine. The only thing we know for sure is that in the United Kingdom a human embryo does not include a human admixed embryo. This precision was introduced to eliminate any possible ambiguity created by the 2007 HFEA decision to license the creation of part-human cytoplasmic hybrid embryos (embryos created by inserting human nuclei into enucleated nonhuman animal eggs) (Human Fertilisation & Embryology Authority, 2007a). Relying on the decision in *R. (Quintavalle) v Secretary of State for Health*, which defined a human embryo as "a live human organism containing within its cell or cells a full set of 46 chromosomes with the normal potential to develop" (House of Lords et al., 2003:43), the HFEA determined that since part-human cytoplasmic hybrid embryos would contain a full human genome they would fall under its regulatory remit (Human Fertilisation & Embryology Authority, 2007b:11). The new legal definition of the human embryo in the HFE Act 2008 excludes the cytoplasmic hybrid embryo but, at the same time, expands the licensing authority of the HFEA to include this category of research.

All told, pursuant to a license granted by the HFEA, human embryo research can proceed in the United Kingdom with few limitations. Explicit prohibitions include: research beyond the appearance of the primitive streak (United Kingdom, 1990:3, 3.(a)); research involving the transfer of a human embryo into a non-human animal (United Kingdom, 1990:3, 3.(b)); and research involving the transfer to a woman of an embryo other than a permitted embryo (as defined in law) (United Kingdom, 2008:3,2 (a) and 4A(1)).

To put all of this in perspective, the regulation of human embryo research in the United Kingdom is not particularly concerned with the point at which the human embryo comes into existence, or the means used to bring about its existence, but rather is concerned with the source of the material from which the embryo is derived—namely, human versus non-human material(s). Beyond this, the regulations are informed by the Warnock report, which held a gradualist position on the moral status of the human embryo (Corrigan et al., 2006). While the human embryo is clearly of the human species in all of its developmental stages, in its earliest developmental stages it is only potentially a human person. For this reason it does not enjoy the full rights of the human person and so may be used for research purposes until the appearance of the primitive streak (and "not later than the end of the period of 14 days beginning with the day on which the process of creating the embryo began" United Kingdom, 2008:3,4). As Beckmann explains the 'logic' of this position:

> In its [the embryo's] first two weeks, its right to protection is consequently not yet as great as it will be in later stages; the early embryo's right to a guarantee of life is therefore assessable over against other important moral values, such as help for patients with life-endangering diseases that are possibly curable only by using therapies developed in embryonic stem cell research. (Beckmann, 2004:612)

In UK law, what tracks moral concern with respect to human embryos is not so much grounded in 'what an embryo is', but in 'how it is to be treated' (*cf.* Beckmann, 2004). On this model human embryo research is *prima facie* ethically acceptable, with the proviso that the pursuit of this research must be justified

against 'special respect' owing to human embryos, not their unconditional worth (Steinbock, 2001).

The United States

In sharp contrast, there is no federal law in the United States governing human embryo research except insofar as there is public law prohibiting the use of funds from the Department of Health and Human Services (HHS) for human embryo research. This law, in the form of an appropriations bill rider, was passed by the United States Congress in 1996 (United States, 1996). The rider, known as the Dickey Amendment, is significant because HHS funding includes funding for the National Institutes of Health (NIH)—the US federal agency primarily responsible for biomedical and health-related research. Since 1996 the rider has been included in the annual Appropriations Acts for HHS. Over the years, the relevant text has hardly changed (Johnson & Williams, 2007:7, note 21). Currently, it reads as follows:

> (a) None of the funds made available in this Act may be used for: (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. (National Institutes of Health, 2009a)

45 CFR 46 is a reference to the Code of Federal Regulations for the protection of human subjects, where "human subject means a living individual" (Department of Health and Human Services, 2005).

Owing to this legal provision, Thomson's ground-breaking research that resulted in the derivation of the first hESC lines was funded by a private firm—Geron. In the wake of this research success, the NIH asked for a legal opinion as to whether NIH funds could support future research to study hESCs (as contrasted with research to derive hESCs). Early in 1999, Harriet Rabb, then General Council of the HHS, argued that the Dickey Amendment did not apply to hESC research. In a memorandum entitled "Federal Funding for Research Involving Pluripotent Stem Cells", dated January 15, 1999, and addressed to Harold Varmus (then-Director of NIH), Rabb reasoned that the "statutory prohibition on the use of funds appropriated to HHS for human embryo research would not apply to research utilizing human pluripotent stem cells because such cells are not a human embryo within the statutory definition"(1999:1). The definition in question refers to embryos as "any organism, not protected as a human subject under 45 CFR 46" (Rabb, 1999:2). Citing the McGraw-Hill Dictionary of Scientific and Technical Terms where the term 'organism' is defined as "an individual constituted to carry out all life functions" (Parker, 5th edition, 1994 qtd. in Rabb, 1999:2), Rabb further argued that:

> Pluripotent stem cells are not organisms and do not have the capacity to develop into an organism

> that could perform all the life functions of a human being—in this sense they are not even precursors to human organisms. They are, rather, human cells that have the potential to evolve into different types of cells such as blood cells or insulin producing cells. (1999:2-3)

In practical terms, this ruling meant that research to derive hESCs was not eligible for federal funding, but that research to study hESCs (previously derived using other funds) was eligible for federal funding (National Research Council (United States) et al., 2007:24).

On August 9, 2001 this all changed. Then-President Bush announced that NIH funds could not be used to study hESCs where the derivation process was initiated after 9:00 P.M. EDT on August 9, 2001. In restricting federal funding in this way, the President reasoned that "the life-and-death decision" to initiate the derivation process had already been made with existing hESCs and so research with these cell lines would be permitted. On a go forward basis, however, there would be no indirect incentive to create and then destroy embryos for the purpose of deriving hESCs for future research using NIH funds. In addition, the Bush administration stipulated that:

> The stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed. Informed consent must have been obtained for the donation of the embryo and that donation must not have involved financial inducements. (National Institutes of Health, 2009b)

In implementing President Bush's policy, the NIH created the Human Embryonic Stem Cell Registry listing all hESC lines meeting the stipulated conditions (National Institutes of Health, 2009c). And, until this Presidential decree was revoked by President Barack Obama, only research on hESCs listed in the Registry was eligible for federal funding.

On March 9, 2009, President Barack Obama lifted the ban on federal funding for embryonic stem cell research (United States, 2009), thereby paving the way for the NIH to fund ethically derived hESCs. Of note, the 2009 NIH *Guidelines on Human Stem Cell Research* return to the earlier (1999) reasoning at NIH to the effect that "[a]lthough hESCs are derived from embryos, such stem cells are not themselves embryos." (National Institutes of Health, 2009d Section II).

Meanwhile, to this day there is no federal policy governing hESC research conducted in the private sector. In the absence of such policy, a patchwork of regulations has evolved at the state level (Moreno & Hynes, 2005). Some states, (notably, California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York and Wisconsin) have enacted laws and funding strategies to promote hESC research (Vestal, 2008). Other states (Arkansas, Indiana, Louisiana, Michigan, North Dakota and South Dakota) have enacted laws to restrict hESC research (Vestal, 2008).[2]

Given the combined absence of federal, and in many instances, state policies governing privately-funded hESC research, in 2005 the National Academies published voluntary guidelines for deriving, handling and using hESCs (National Research Council (United States) et al., 2005). These *Guidelines for Human Embryonic Stem Cell Research*, as amended in 2007 (National Research Council (United States) et al., 2007), are extremely permissive (Robert & Baylis,

2005). Among the few restrictions on hESC research is the internationally recognized 14-day limit on human embryo research. Specifically, the *Guidelines* recommend against "[r]esearch involving in vitro culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first" (National Research Council (United States) et al., 2007: Appendix A, 1.2(c)(1)).

The 2005 *Guidelines* define the embryo as:

> An animal in the early stages of growth and differentiation that are characterized by cleavage, laying down of fundamental tissues, and the formation of primitive organs and organ systems; especially the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes known as a foetus. (National Research Council (United States) et al., 2005:116)

This definition of the human embryo contrasts markedly with the definition in the Dickey Amendment wherein it is stipulated that "human embryo includes any organism, not protected as a human subject under 45 CFR 46." With the 2005 *Guidelines*, the human embryo only comes into being at the time of implantation, some two weeks after fertilization. Nonetheless, these *Guidelines*, and the subsequent 2007 *Amendment to the Guidelines*, sometimes use the term embryo in the vernacular to refer to "all stages of development from fertilization until some ill-defined stage when it is called a foetus" (National Research Council (United States) et al., 2005:116). Preferentially, however, the term 'blastocyst' is used "to refer to the stage of embryonic [sic] development from which hES cells are obtained" (National Research Council (United States) et al., 2007:4).

For President Bush the human embryo is understood and valued in terms of its potential to become one of us. In his words, "Like a snowflake, each of these embryos is unique, with the unique genetic potential of an individual human being" (2001). By comparison, federal policy in the United States is more circumspect insofar as there is no particular attention to the potential of the developing human embryo. If the human embryo were deserving of legal protection on the basis of potentiality, then logically the federal government would have to regulate both the public and private spheres of research. At present, the federal government only regulates the use of public funds for human embryo research and does not prohibit human embryo research in the private sector.

For its part, the National Academies attach no importance to the means by which the human embryo is created, but insist that, notwithstanding common parlance, the term human embryo properly applies to the human organism only from the time of implantation (approximately 14 days) (National Research Council (United States) et al., 2005:116). Prior to this stage there is the zygote, the morula and the blastocyst, all of which are legitimately available for research.

In summary, in the United States, federal funding for human embryo research is prohibited in the Appropriations Acts for HHS. Beyond this, there is a fractured and politicized environment in which some claim absolute protection of the human embryo from destructive research, while others advocate a gradualist approach to

moral status that would allow for limited embryo research, including research to derive hESCs.

Germany

In Germany embryo research, including research to derive hESCs, is illegal (Deutscher Bundestag, 1990). The German Constitutional Court has determined that, "wherever there is human life, it has human dignity" (VerfGE 88, 203; 1999:251f. qtd. in Beckmann, 2004:615).[3] And, article 1 of the German Constitution establishes that: "the dignity of the human being is inviolable" (qtd. in Beckmann, 2004:615). Building on the values entrenched in the German constitution, *The Embryo Protection Act* (1990), prohibits any interventions on, or manipulations of, the human embryo "for a purpose not serving its preservation" (Deutscher Bundestag, 1990:2(1)). According to the *Act* "an embryo already means the human egg cell, fertilised and capable of developing, from the time of fusion of the nuclei, and further, each totipotent cell removed from an embryo that is assumed to be able to divide and to develop into an individual under the appropriate conditions for that" (Deutscher Bundestag, 1990:8(1)). As such, German legislation on embryo research (which includes two definitions of an embryo—(i) a fertilised egg and (ii) a totipotent cell removed from an embryo)—is more restrictive than legislation in either the United States or the United Kingdom.

In March 1999, just shortly after Thomson announced that he had successfully derived hESC lines, the *Deutsche Forschungs-gemeinschaft* (DFG), Germany's main federal research foundation, published a statement against the use of hESCs (regardless of whether the embryos were created by *in vitro* fertilization or cloning) on the grounds that hESCs come from human embryos that are otherwise capable of developing into human beings. As Heinemann and Honnefelder observe: "the DFG opinion relied on the criteria of totipotency as the basis of its ethical argument" (2002:531-532). In a subsequent statement in May 2001, the DFG noted that *The Embryo Protection Act* applied only to embryos and totipotent cells, and that as hESC lines were not themselves totipotent, but merely pluripotent, they would not be subject to the *Act* (Heinemann & Honnefelder, 2002). On this reasoning, the DFG recommended allowing the importation of pluripotent hESCs from foreign countries for research involving the study, but not the derivation, of hESCs.

In 2002, the German Parliament passed the *Stem Cell Act* allowing German researchers to import hESCs for research under strict conditions. The proposed hESC research must be for 'high-ranking objectives' that could not be pursued by other means.[4] The embryos of origin (from which the imported hESCs lines will have been derived) must have been created by in vitro fertilization for reproductive purposes and must have been deemed in excess of clinical need for reasons related to the wishes of the embryo providers, and not for "reasons inherent in the embryos themselves". As well, the embryo providers must have given free and informed consent for the research use of their embryos without honorarium or other financial incentives (Deutscher Bundestag, 2002:4(2)1.a, b, c). In addition to all of the above, the imported hESC lines must have been derived before January 1, 2002 (the time at which the *Stem Cell Act* came into force) in the country of origin, in accordance with relevant national legislation. Recently the

cut-off date has been moved to May 1, 2007 (Die Bundesregierung, 2008).[5] The rules governing the importation of hESC lines into Germany remain unchanged, however, as does the prohibition on deriving hESC lines.

Despite what some perceive as a recent liberalization of German law, it is important to note that the intentions with which human embryos are created, and the means of creation, retain strong ethical relevance in the German effort to establish legal standards for human embryo and hESC research (Heinemann & Honnefelder, 2002). In the 2002 *Stem Cell Act*, "embryo means any human totipotent cell which has the potential to divide and to develop into a human being if the necessary conditions prevail" (Deutscher Bundestag, 2002:3(4)). In Germany, there is a clear concern with potentiality as that which is definitive of embryos, with little (no) concern to discriminate between embryos according to the means by which an organism with such potential might come into being.

As with the 2001 decree issued by President Bush for hESC research in the United States, German law entrenches the belief that destroying human embryos to create hESCs is unacceptable, but that using hESCs derived by others (where Germany is not complicit with the decision to destroy human embryos) is permissible under certain conditions. In contrast with the United States, however, Germany has legal (including criminal) sanctions that apply to both the private and public sectors with a view to preventing the destruction of human embryos by scientists working in Germany. According to Beckman (2004) and others (*cf*. Sperling, 2008: 364-365 & nt.3), German law is uniquely concerned not only to assert a very robust moral status for the human embryo, but also to extend greater protections to the *in vitro* human embryo because of its greater state of vulnerability and greater exposure to misuse. A recent posting by the Bundesregierung on embryo protections in Germany, states: "The fundamental values enshrined in the German Basic Law, or constitution, of human dignity and the right to life extend protection to unborn human beings, even at the embryonic stage" [emphasis added] (Die Bundesregierung, 2008).

The troubled word 'embryo'

A brief comparison of the different legal understandings of the term 'embryo' as entrenched in different jurisdictions that either permit or prohibit human embryo research reveals the absence of any kind of agreement on what a human embryo is. In the United Kingdom the pivotal question appears to be: 'What key features describe the human embryo?' The answer given is: "live", "human", and not "admixed", able to be created by fertilization or any other process (United Kingdom, 2008:1,1(a) and 1,2(a)). Whatever potential the human embryo might possess is not mentioned in any definition of the embryo and, in any event, is clearly insufficient to merit legal protection from destructive research until the appearance of the primitive streak. Prior to this developmental stage, the "live", "human" embryo is available for research use.

In the United States the key question appears to be: 'Where does the human embryo come from?' The answer given is: "fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." Notably, this definition of the human embryo fails to provide any explanation of what an embryo actually is 'in kind'. While former President Bush clearly

believes that human embryos have unique potential, and for this reason ought not to be destroyed in research, there is no federal law prohibiting human embryo research *per se*. All that is prohibited is public funding of human embryo research involving human organisms created by "fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells" (Bush, 2007:3(a)).

Lastly, in Germany, the question is: 'What can the human embryo do?' The answers given are: "develop into an individual under the appropriate conditions," and "develop into a human being if the necessary conditions prevail." With these nearly identical definitions of the embryo what matters is the organism's or cell's potential to become a fully developed human being (however created and regardless of the conditions necessary for the potential to be expressed) (Deutscher Bundestag, 1990:8(1); Deutscher Bundestag, 2002:3(4)). Under German law, human embryos carry "special status," and their potential is regarded as best expressed if used for the embryos' own (inbuilt) purposes: hence the prohibition in *The Embryo Protection Act* (1990) against any manipulation of human embryos for any purposes that do not serve their preservation. For this reason, Germany has taken steps to secure legal protections for human embryos against any and all destructive research.

Significantly, in jurisdictions like the United States and Germany that prohibit (some) research to derive hESCs, yet permit research to study existing hESCs, human embryos must remain distinguishable from hESCs in terms of their potential. This explains the importance attributed to the distinction between totipotent and pluripotent cells. In the American context we see this distinction outlined in the legal opinion generated by Rabb:

> Pluripotent stem cells are not organisms and do not have the capacity to develop into an organism that could perform all the life functions of a human being—in this sense they are not even precursors to human organisms. They are, rather, human cells that have the potential to evolve into different types of cells such as blood cells or insulin producing cells. (Rabb, 1999:2-3)

In the German context, we can point to the following clear statement by the *Nationaler Ethikrat*[6]:

> The stem cells themselves are not embryos within the meaning of [T]he Embryo Protection Law [i.e. *The Embryo Protection Act* (1990)], as the general scientific presupposition today is that these cells are not totipotent but pluripotent—that is, they do not possess the capacity to develop into a human being. The import and use of embryonic stem cells for research purposes are to be regulated by a Stem Cell Law. (Nationaler Ethikrat, 2008a)

As evidenced by the above statements, in the debate about the ethics of hESC research it very much matters that human embryos are totipotent cells (cells that have "the ability to give rise to all the cell types of the body plus all of the cell types that make up the extraembryonic tissues such as the placenta") (National Institutes of Health, 2009e), whereas hESCs are merely pluripotent cells (they have "the ability to give rise to all of the various cell types of the body … [but]

cannot make extra-embryonic tissues such as the amnion, chorion, and other components of the placenta.") (National Institutes of Health, 2009f) (see comments by Rabb, above). But is this stipulated distinction between embryos and hESCs accurate? And, is it true that hESCs cannot differentiate into extra-embryonic tissues such as the placenta? Not according to Lee Silver who cites work by Thomson, the pioneer of both hES and iPS cell research. As Silver notes, in the original publication describing the initial success in deriving hESCs (and in subsequent publications), Thomson has reported that hESCs are capable of differentiating into trophoblast cells, which are precursors to the placenta (Silver, 2008). Add to this Thomson's most recent research on iPS cells (Yu et al., 2007), which suggests that all somatic cells (not just hESCs) may be totipotent if the necessary conditions prevail, and one cannot help but wonder: 'What is a human embryo and how will we know one when we see one?'

An embryo is an embryo is an embryo[7]

Increasingly, the hESC debate is the site of knowledge production (*cf.* Parry 2009 and Testa, 2008) for what can and should count as a human embryo. As this field of research has expanded, so too have the definitions of the term 'human embryo'—this, in an effort to either broaden or restrict the scope of permissible research. To be sure, much is at stake in the debate about what counts as a human embryo deserving of protection. According to hESC enthusiasts, the very future of regenerative medicine—the health and human welfare of present and future patients—hangs in the balance. According to others, nothing less than our humanity is at stake if we should proceed to mine the human embryo for stem cells, and forsake our moral obligation to treat all human beings as equal in basic dignity and human rights (see Squier & Waldby, 2005; Waldby, 2002).

In recent years, as the ethical debate about the moral status of the developing human embryo has intensified, many, including "scientists who may not necessarily have strong feelings about the matter have come to believe that 'embryo equals ethical problems'"(Mauron & Jaconi, 2007:2). As a result, in an effort to sidestep the ethical debate, some stem cell scientists have used discursive strategies to "convert societal issues into technical ones and, at the same time, expel other groups or framings from policymaking processes. Thus human embryos are described according to their technical characteristics, their visual appearance as cell-like, and clearly demarcated from foetuses" (Parry, 2009:109). As well, some stem cell scientists have tried "to make concessions to assuage the moral reservations of a sizable minority" (Snyder et al., 2006:399; *cf.* Testa, 2008). These scientists have invested their talent and resources to develop alternate (hopefully less ethically controversial) sources of human pluripotent stem cells including parthenogenesis, somatic cell nuclear transfer, single-cell embryo biopsy, altered nuclear transfer, discarded poor quality IVF embryos, and, most recently, reprogramming somatic nuclei (Baylis, 2008; Green, 2007).

In November 2007, Yamanaka and colleagues at the University of Kyoto reported reprogramming cells from the facial skin of a 36-year-old woman and the connective tissue of a 69-year-old man (Takahashi et al., 2007). At the same time, a team led by Thomson at the University of Wisconsin reported reprogramming

cells from foetal skin and the foreskin of a newborn boy (Yu et al., 2007). Both teams confirmed that the iPS cell lines satisfied the criteria for hESC lines. Controversy remains, however, not only in the realm of science, but also in the realm of ethics.

Some clearly recognize that "for those who believe it is unethical to destroy human preimplantation embryos, finding other paths toward pluripotency is a positive move forward" (International Society for Stem Cell Research, 2007b). For this reason, they applaud iPS cell research. For example, according to Ian Wilmut at the University of Edinburgh (part of the team that cloned Dolly the sheep in 1997): "We can now envisage a time when a simple approach can be used to produce stem cells that are able to form any tissue from a small sample taken from any of us" (Sample, 2007). Robert Lanza of Advanced Cell Technology is even more elated: "This work represents a tremendous scientific milestone—the biological equivalent of the Wright Brothers' first airplane.... This is truly the Holy Grail—to be able to take a few cells from a patient—say a cheek swab or few skin cells—and turn them into stem cells in the laboratory" (Keim, 2007).

Amidst the elevated levels of enthusiasm, there is also a sense of relief. Beleaguered stem cell biologist José Cibelli of Michigan State University notes: "the whole field is going to completely change. People working on ethics will have to find something new to worry about" (Vogel & Holden, 2007). Another crucial vote of confidence comes from James Battey, the current Vice Chair of the NIH Stem Cell Task Force: "I see no reason on Earth why this would not be eligible for [US] federal funding", "I think it's a wonderful new development" (Weiss, 2007:A01).

Others are somewhat more guarded in their praise, however, lest their enthusiasm undermine public and financial support for research on hESCs and cloning. For example, Alan Leshner and James Thomson, caution that: "We simply cannot invest all our hopes in a single approach. Federal funding is essential for both adult and embryonic stem cell research, even as promising alternatives are beginning to emerge" (Leshner & Thomson, 2007). For all the promise that iPS cells represent as a valuable research tool and future potential therapy, they also represent a clear and present danger to research in which the hESC community is heavily vested. The perceived threat is evident in the following excerpts of statements issued by the International Society for Stem Cell Research (ISSCR):

> The ISSCR emphasizes that these findings [from iPS cell research] do not obviate the need for research using human embryonic stem cells; rather the different avenues of human stem cell research should be pursued side by side providing complementary information. Indeed, these advances in iPS cell research draw on the many years of embryonic stem cell research. (International Society for Stem Cell Research, 2007a)

> It is premature to suggest that the use of iPS cells can replace the derivation of embryonic stem cells from embryos or by nuclear transfer. We believe that research on human embryonic stem cells, somatic cell nuclear transfer and 'adult' or tissue-specific stem cells needs to continue in parallel. (International Society for Stem Cell Research, 2007b)

> The breakthrough in iPS cell research was made possible by several years of

> prior embryonic stem cell research. Embryonic stem cell research must continue if scientists are going to have the most modern and powerful research tools at their disposal. (International Society for Stem Cell Research, 2008)

In contrast, opponents of hESC research wax lyrical about the end of stem cell research using human embryos. For example, Bishop Elio Sgreccia, president of the Pontifical Academy for Life, stated in a Vatican Radio interview:

> I do not know if those who have invested money and passed laws precisely to allow this [embryonic stem-cell research] will be able to recognize their error and turn back, but at least the scientists who want to achieve results will go looking where they have been proven to be found. (O'Brien, 2007)

Also from a Catholic perspective, Father Thomas Berg, executive director of the Westchester Institute for Ethics and the Human Person, noted that:

> … reprogramming clears the bar in terms of reasonable concern for human dignity in biotech research: Never at any point in the process of reprogramming is there ever a danger of involving—even accidentally we might say—techniques that could bring about a human embryo, as would happen in cloning. The science of pluripotent stem cell research can move forward toward therapies and cures in a manner that is free of any ethical concerns. (Anderson, 2007)

No less enthusiastic is Leon Kass, past Chair of the President's Council on Bioethics. In his view,

> Reprogramming of human somatic cells to pluripotency is an enormously significant achievement, one that boosters of medical progress and defenders of human dignity can celebrate without qualification. The evidence … is complete and compelling: Cells as versatile and useful as embryonic stem cells, obtained without embryo creation and destruction or the need to exploit women for eggs. … The ethical and political benefits may be equally great. (Condic et al., 2007)

Finally, Charles Krauthammer, past member of the President's Council on Bioethics, has confidently predicted that:

> Even a scientist who cares not a whit about the morality of embryo destruction will adopt this technique [iPS cell research] because it is so simple and powerful. The embryonic stem cell debate is over… scientific reasons alone will now incline even the most willful researchers to leave the human embryo alone. (Krauthammer, 2007:A23)

Behind all of these bold assertions, however, is the assumption that we actually know what a human embryo is and that iPS cells are not themselves embryos. But what if human skin cells converted into iPS cells ultimately prove to be totipotent cells and, as such, are just another kind of human embryo? According to Kaebnick:

> it is too early to say definitively that the new entities [iPS cells] are not embryos. If reprogramming through cloning creates a new sort of embryo,

> different from natural human embryos in important ways, then this new kind of reprogramming might prove to be creating *yet another* new kind of embryo. (Kaebnick, 2008)

With iPS cells, scientists have shown us that by adding a few gene transcription factors every somatic cell has the potential to generate pluripotent stem cell lines and more than that, with further manipulation these same cells could perhaps become totipotent—capable of developing into a human being.

Thus far, the science of iPS cell research has been greeted with considerable fanfare including international headlines celebrating the prowess of scientists who have managed to generate pluripotent stem cell lines without using human embryos. But is the *New York Times* headline "Scientists Bypass Need for Embryo to Get Stem Cells" (Kolata, 2007) accurate? If a human embryo is defined as "live" and "human", able to be created by fertilization or any other process (as in the *HFE Act 2008*) or is defined as "any human totipotent cell which has the potential to divide and to develop into a human being if the necessary conditions prevail" (as in the German *Stem Cell Act*), then this and similar headlines might be both erroneous and misleading. While it is certainly true that iPS cells are generated without using embryos (defined in terms of origin), they themselves may be embryos (defined in terms of potential) —in which case iPS cell research would involve the use of human embryos. Moreover, this type of research will inevitably thwart the "embryo's" potential to generate a new human being.

At the heart of the matter is whether 'so-called' pluripotent stem cells (whether hESCs or iPS cells) are potentially totipotent. William Neaves, for example, insists "that when one directly reprograms an ordinary body cell … one has transformed that ordinary skin cell into the functional equivalent of a fertilized egg" (Humphrey, 2008). Not so, according to others. For example, Cynthia Cohen and Bruce Brandhorst insist that "neither ES cells nor iPS cells have been shown, or are expected to be shown, to be equivalent to embryos… they … (1) lack the extracellular layers required by embryos, (2) are too small and lack egg-like organization, and (3) are not totipotent, by all evidence" (Cohen & Brandhorst, 2008). On this view, ES cells and iPS cells are not totipotent—they are not capable of generating extra embryonic tissue, such as the placenta. According to Silver, however, Cohen and Brandhorst (like many others) are mistaken insofar as "the available data do not rule out the possibility that ES cells (and iPS cells) are totipotent" (Silver, 2008). This much Cohen and Brandhorst acknowledge; nonetheless, they insist that "no one has shown that human ES cells can produce trophoblast and inner cell mass cells in a dish that will then organize themselves into a blastocyst that could implant and develop. The same is true of human iPS cells" (Silver, 2008). This is indeed true, as the proposed research would never be approved by a research review committee. What then can we 'know' about the potential of hESCs and iPS cells that might shed light on their status as embryos, understood in ethical, not biological, terms?

Throwing down the gauntlet

In recent years, stem cell science has shown us that it is possible to impose pluripotency on human somatic cells. Now, this same science is poised to show us that it may also be possible to impose totipotency on human somatic cells.

With this prospect (exciting for some, and frightening for others), science has thrown down the gauntlet. Indeed, as Bernard Baertschi and Alexandre Mauron point out:

> the more it becomes obvious that somatic cells have the capability to be restored to the ES cell state and the more indistinguishable embryonic cells become from somatic cells in terms of potentialities, the harder it becomes to see what is so special, in ethical terms, about embryonic cells and embryos. There is a deep irony here: the more one envisions doing away with human embryos in stem cell research—thus 'solving' the ethical problem in the view of many scientists and politicians—the less convincing seem the arguments that made embryo research ethically disturbing in the first place. (2008:2)

To date, the pluripotent/totipotent distinction has been relied upon in many jurisdictions (including the United States and Germany) in debates on hESC research in order to distinguish between cells that may be used for research (pluripotent cells), and cells that may not be used for research (totipotent cells). But, if all human somatic cells can be made totipotent (viz., with the potential to develop into human beings), then what sense is there in insisting on a moral demarcation line between human embryos and human somatic cells that is based on potentiality? Furthermore, if there is no such moral demarcation line, what then? Do we embrace the *reductio ad absurdum* where all body cells are afforded special protection(s) by virtue of their potential to become human beings? Alternatively, do we strip conventional human embryos of any claim to special moral status and treat them no differently than human somatic cells? Or, do we look for a different demarcation line on the basis of which to draw moral distinctions between different human cells?

One response to this last question involves discriminating between human embryos (defined in terms of their capacity to develop into human beings) on the basis of their 'natural potential' (viz., what human embryos are capable of becoming based upon their own internal forces for change if not unduly interfered with, and if placed in a environment conducive to continued growth and development), and their 'artificial potential' (viz., what human embryos may be capable of becoming by virtue of external interventions and placement in a novel environment conducive to continued growth and development) (DeGrazia, 2006). On this distinction, human iPS cells *qua* human embryos would be distinguishable from conventional human embryos in that their capacity for totipotency—their ability to develop into human beings—is not inherent, but is the result of external manipulations. On this view, while iPS cells *qua* embryos and conventional embryos may both be technically totipotent, iPS cells are not deserving of special protection(s) as their totipotency requires a reconfiguration of their biology and their natural environment for them to develop into human beings. But as David DeGrazia (2006) asks, why should 'natural potential' matter in a way that 'artificial potential' does not? Moreover, if 'natural' means, 'normal' as in 'most likely to occur', then how are we to reconcile this with, the fact that, "[t]he normal reproductive biology of human beings is such that 75 percent of all *naturally* fertilized eggs will succumb to death *naturally* before the nine-month period

of gestation is completed" (Silver 1997: 43) As Lee Silver concludes: "It is the odd egg only that develops into a live-born baby" (1997:43). In the alternative, if 'natural' means, 'as a result of fertilization', then what are we to make of future human embryos that may be created through the use of novel reproductive technologies such as cloning should these embryos have the same developmental potential as conventional embryos?

Another response to the question about alternate moral demarcation lines suggests that what matters morally is not what embryos are or can do (in their own right or with external assistance), but rather what they were made for. On this view, what is deserving of moral regard is the intentions of the person(s) who created the "live, human, not admixed embryos" (United Kingdom) by means of "fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells" (United Kingdom and United States) with the capacity "to develop into human beings if the necessary conditions prevail" (Germany). Here, what counts as a human embryo from the perspective of moral status is not a matter of its own internal biological make-up, or potential, but rather is a matter of its relational properties. In other words, its moral status is a function of the purpose(s) imprinted upon it by virtue of the will of its creator(s). Here, human embryos are divested of any inherent moral worth. Indeed, in a recent study reporting on the attitudes of UK and Swiss embryo donors to hESC research, Erica Haimes and colleagues (2008) found, in response to the question "What is an embryo?" that "embryos are not fixed, universal biological entities but are defined by, and acted upon in relation to, their social context, that is, by their location in time and space" (Haimes et al., 2008:124).[8]

In closing, we do not yet know for certain that somatic cells can be transformed into totipotent cells, but clearly the prospect is there. This makes it all the more urgent that we look to clarify what features of conventional human embryos might render them deserving of protection from destructive research so that we might better understand whether such protection is also owed to other cells and organisms not traditionally conceived of as embryos, or whether such protection of conventional embryos is misguided.

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Notes

[1] For a noteworthy exception, see Maienschein, (2007).

[2] For a summary of state legislation on stem cell research, see the National Conference of State Legislatures [On-line] http://www.ncsl.org/programs/health/genetics/embfet.htm

[3] Krones *et al.* (2006) have noted that: "German constitutional law tends to encourage a categorical view of new developments, since technologies and actions are initially judged from the top-down according to the first two universal, supreme principles of the German Constitution, which are the protection of human dignity and right to life of every human being (Articles 1 and 2 of the Constitution (Grundgesetz)), rather than evaluated in more context-specific manner of case law" (3).

[4] The legislation describes high ranking research objectives as follows: "1) such research serves eminent research aims to generate scientific knowledge in basic research or to increase medical knowledge for the development of diagnostic, preventive or therapeutic methods to be applied to humans; and that, 2) according to the state-of-the-art of science and technology, (a) the questions to be studied in the research project concerned have been clarified as far as possible through in vitro models using animal cells or through animal experiments and (b) the scientific knowledge to be obtained from the research project concerned cannot be expected to be gained by using cells other than embryonic stem cells" (Deutscher Bundestag, 2002:5).

[5] See Sperling (2008) for a discussion of how each of these requirements "carries a special moral charge in Germany" (367).

[6] This is an interdisciplinary body whose members (up to twenty-five at one time) are appointed by the Federal Chancellor. It has been influential in shaping the course of stem cell politics in Germany (Heinemann &

Honnefelder, 2002; Nationaler Ethikrat, 2008b).

[7] This phrase is borrowed from Gertrude Stein's poem *Sacred Emily* in which the sentence "Rose is a rose is a rose is a rose" appears (Stein, 1999). This sentence is now commonly interpreted to mean 'things are what they are.'

[8] For discussions of how embryos are defined by and acted upon in relation to their situated social context see Franklin (2001), Krones (2006), Kim (2008), Parry (2006) and Williams *et al.* (2008).

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