Commentary

# The debate surrounding human embryonic stem cell research in the USA

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## Abstract

Despite its potential for reducing human suffering, the advancement of human embryonic stem cell research has not been given top priority by the US government, and the scientific community has been engaged in a debate on this issue in the USA and beyond. The central question in this debate is whether the promise of stem cells justifies the destruction of human embryos – mainly embryos that are surplus to the needs of patients undergoing infertility treatment. It is argued here that this debate belongs in the same category as the debates on global warming and evolution, because it has much in common with both. It is conducted with a heavy load of scientifically uninformed views and beliefs and framed largely by an implacable opposition with the aim of creating public confusion and doubt. It is primarily politically motivated and, as is true about the debate on evolution, it is rooted in religion. A human embryo is not a human being or person even if it is deserving of – and receives – respect and extraordinary care in the context of assisted human reproduction. Rather than engaging in a futile debate that clouds the way forward in a vital branch of biology, scientists ought to continue to emphasize the importance of human embryo research.

***Keywords:*** *donation, embryo, human, IVF, stem cells, transplantation*

## Introduction

The inner cell mass of the human blastocyst contains cells that are pluripotent. When they are isolated from surrounding trophectoderm and placed under the right conditions *in vitro*, they are able to differentiate into all cell types in the adult body. These human embryonic stem cells (ESC) can be propagated indefinitely and used as a source of cells and tissues for transplantation, to assist in developing and testing new drugs, and to study disease and its progression (reviewed by Trounson, 2006). The main source of human ESC currently is surplus frozen human embryos donated by patients undergoing in-vitro fertilization (IVF) for infertility treatment.

## Conflicts between the US government and the US scientific community

Despite its potential to provide treatment options for a host of debilitating diseases and conditions, advancement of human ESC research has not been granted top priority by the US government. This has led the US scientific community to engage in a debate on the issue. The central question in this debate is whether the promise of stem cells justifies the 'destruction' of human embryos. A powerful and influential minority, which includes the current President of the United States, thinks not. Mr Bush has rejected both the advice of the (former) Director of the National Institutes of Health (NIH) and an offer of guidance from the (former) Surgeon General on the subject (Harris, 2007). He has argued for 'a culture of life where the strong protect the weak and where we recognize in every human life the image of our creator'. Thus, on the basis of this unabashedly religious point of view, and by attaching highly restrictive conditions to governmental funding, the US government has declined to provide adequate support for research in this area (The White House, 2007).

In a defiant move that is symbolic of the general attitude toward the federal government's policy, several state governments have appropriated considerable state funds for human ESC research but, on a national level, the problem remains unresolved.

There are differing opinions among scientists on how to respond to this situation. One opinion, which appears to be that of the majority, was articulated by Snyder *et al*. (2006) as follows: 'In a pluralistic society, it is not unreasonable to make concessions to assuage the moral reservations of a sizable minority'. This suggests that scientists should accept the imposition of arbitrary restrictions on research, and devote resources and effort to changing the course of a scientific endeavour to comply. But as Dick Taverne of the House of Lords in the UK has commented: 'The fact is that science, like art, is not a democratic activity. You do not decide by referendum whether the earth goes around the sun'. (Taverne, 2004). An even more relevant response is the following by bioethicist, Ronald M Green (2001): 'a pluralistic democracy, committed to protecting and improving the health of its citizens, cannot justly deny [support to] one area [of] research merely because some of its citizens object to that research based on personal religious and moral beliefs. Unless objections can be grounded in concerns appropriate to the pluralistic democracy – and this means reasonably clear



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issues of public health and safety – they must be set aside'. (Green, 2001).

One could go a step further and claim that this debate, the basis of which is the belief that a human embryo is a human person, is ludicrous and hypocritical, and scientists should call it just that instead of focusing their efforts on making concessions that run contrary to the whole *raison d'etre* of science. It is ludicrous to claim, as does the Pontifical Academy for Life (2004), that human embryos are 'the innocents of our time' or 'sacrificial victims to be immolated on the altar of science'.

A more reasonable definition of a human embryo in the light of modern cell biology, embryology and emerging reproductive technologies is one offered recently: 'a discrete entity that has arisen from: (i) either the first mitotic division when fertilization of a human oocyte by a human sperm is complete; or (ii) any other process that initiates organized development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears' (Findlay *et al*., 2007).

Moral philosophers debate the meaning of the term 'human being' and suggest that potentiality and identity together constitute personhood and give a serious right to life (cf. Lockwood, 2005). They have argued the moral status of the human embryo as a 'special entity, a composite between a person and an object', which, they reason, 'deserves respect and protection, but, if it is not going to develop into a child, it can be used for research, for therapeutic purposes, or destroyed' (Dragona-Monachou, 2007).

For the purposes of the present argument, it suffices to say that a human embryo is not, as President Bush has said (Bush, 2005), 'like every other human being'. A human embryo is neither a human being nor a person.

## The search for alternative sources of human ESC

Are any concessions possible or reasonable in this debate? Since it is the use of viable embryos as the main source of human ESC that fuels the debate, the search for alternative sources has emerged as one predictable concession. But many of the proposals for such alternative sources are based almost exclusively on public palatability, with scant regard for practicality, feasibility, efficiency, or logic. One such proposal is based on so-called 'altered nuclear transfer', which was conceived by a member of the President's Council on Bioethics (2005). It entails the use of gene silencing or RNA interference technology to inactivate *Cdx2* in the somatic cell that will be used as a donor during nuclear transfer to an enucleated human egg (Hurlbut, 2005). The inactivation of *Cdx2* prevents the formation of trophectodermal cells without affecting the formation of inner cell mass cells thereby producing, according to Hurlbut, 'a limited cellular system that is biologically and morally akin to a complex tissue culture'. This entity would therefore die at a point corresponding to the 'blastocyst' stage (Chawengsaksophak *et al*., 2004), but stem cells could still be derived from it, it is argued, without any ethical burden. Subsequently, *Cdx2* function would have to be restored in the stem cells or their derivatives intended for transplantation by additional genetic manipulations, since, at least in the mouse, this gene is involved in developmental processes other than trophectoderm formation. One simply does not know what the case may be in the human.

Despite the convoluted nature of this proposal (Melton *et al*., 2004), some reputable scientists did undertake the task of demonstrating its feasibility in a mouse model (Meissner and Jaenisch, 2006). However, potential translation of this research to a human model adds another layer of complexity to an already complex experiment. How many human eggs must be accumulated in order to test this hypothesis? Would in-vitro maturation have to be used, as has been suggested? In the context of potential sources of human embryonic stem cells, altered nuclear transfer simply does not make sense.

Other proposals for alternative sources of human ESC have wrapped basic embryology concepts in a language that has no clear scientific meaning or justification. For example, another member of the President's Council on Bioethics advocates the use of so-called 'organismically dead' embryos, which are more accurately described as fresh or frozen–thawed embryos that do not meet viability criteria and are routinely discarded in the course of clinical IVF (Alikani and Willadsen, 2002). Landry and Zucker (2004) compare these embryos to brain-dead persons, arguing that 'the ethical framework currently used for obtaining essential organs for transplantation from deceased adults and children could be extended to cover obtaining stem cells from dead human embryos'. On the basis of this argument, if embryo 'death' were to be defined in absolute terms (Grinnell, 2003), then one could culture the 'dead' embryos further (or take cells from them), produce blastocysts, and derive stem cells with sound moral justification. Several scientific publications have since referred to this proposal, overlooking the fact that it is underpinned by the elevation of the human preimplantation embryo to the status of a human person. It also disregards data accumulated in a quarter century of human IVF that form the basis of embryo selection for transfer and cryopreservation.

At the same time, Landry and Zucker (2004) refer to the category of non-viable as a 'misclassification' and reject the suggestion (Alikani and Willadsen, 2002) that aggregates of potentially viable cells from non-viable embryos that rarely undergo normal blastulation in extended culture might be used as a source of stem cells, since some such aggregates do form blastocysts in culture. Nonetheless, 4 years after the original proposal, the journal *Nature* apparently found the prospect of stem cells from 'dead' embryos noteworthy (Pearson and Abbott, 2006), and reported on a study by Zhang *et al*. (2006) that claimed to have made a novel cell line from a 'late-arrested' embryo.

In their experiments, these authors used 119 arrested day 3–5 embryos (4–10-cell stage) and 13 late-arrested day 6–7 embryos (16–24-cell stage). Of the former, 'four proliferated, but without any clear signs of primary human ESC-like outgrowth' whereas from the latter, one stable human ESC line was derived.

The publishers of the paper by Zhang *et al*. (2006) accepted these authors' claim to have been able to identify what they referred to as 'late-arrested' embryos (so-called 'dead' embryos), i.e. at 16–24 cells, in which 'no blastomere from the embryos had undergone any cleavage division during the last

24–48 h'. This is an interesting claim, but is hindered by the fact that it is difficult to definitively follow the development of each and every blastomere in a 16-24-cell human embryo. After 4 days in culture, it is very rare to find 16-24-cell embryos in which some form of compaction, even if abnormal, has not occurred; compaction obscures total cell number and cell fate. This is confirmed by evidence from the author's embryology database (EggCyte; Tomkin and Cohen, 2001) which contains detailed morphological analysis of >90,000 embryos. It is likely, therefore, that the 'late-arrested' embryos reported by Zhang *et al*. (2006) were not, in fact, arrested and did not actually meet the authors' stated death criteria.

The value of the work by these authors was not in showing that stem cells could be isolated from a 'dead' human embryo; they did, however, confirm that the majority of embryos excluded from transfer or cryopreservation, based on cleavage abnormalities, fail to form blastocysts in extended culture (Alikani *et al*., 2000) without the manipulations described previously (Alikani and Willadsen, 2002), but the few that do blastulate may be useful as a source of stem cells.

Another proposal reported in *Nature* (Klimanskaya *et al*., 2006) caught the attention of practically all major newspapers in the USA: 'non-harmful biopsy of living embryos' as it was dubbed by the President's Council on Bioethics, whereby a single cell is removed from normally developing day-3 embryos during clinical preimplantation genetic diagnosis or screening (PGD or PGS). The biopsied cell is placed under culture conditions that promote its proliferation to the point where stem cells can be extracted (Chung *et al*., 2006; Klimanskaya *et al*., 2006). The article by Klimanskaya *et al*. (2006) starts with the emphatic statement that the biopsy procedure 'does not interfere with the embryo's developmental potential'. This is a contested point among those with clinical PGD experience (Cohen *et al*. 2007; Cohen and Grifo, 2007). Indeed, the removal of a cell from a day-3 human embryo *in vitro,* which on average has fewer than seven cells (and not eight cells as stated often), is unlikely to be entirely without negative effect on the viability of the embryo.

The context of PGD for infertility under the best circumstances is that some potential risk may be tolerated in view of the benefit the procedure offers the patient; outside that context, and with the current technology, blastomere biopsy cannot be justified. On the other hand, if this 'alternative' method were to be used only when PGD is medically indicated and a biopsy is necessary, the cell cannot be assumed to be normal (as it would be in the mouse, for instance), and its propagation in culture is likely to be an inefficient process. Moreover, for therapeutic purposes, the usefulness of cell lines prepared from potentially abnormal embryos for therapeutic purposes is quite limited, at least at this point.

Other more interesting and reasoned efforts to generate human ESC bypass the need for the often scarce human eggs and/or embryos altogether and overcome the issue of histocompatibility without having to resort to somatic cell nuclear transfer (reviewed by Yamanaka, 2007). The potential utility of such methods, were they to be fully developed, cannot be disputed. They include the reprogramming of somatic cells to express stem cell properties through cell fusion technology (Do and Scholer, 2005; Cowan *et al*., 2005; Strelchenko *et al*., 2006) and, more recently, through genetic manipulation (Okita *et al*., 2007; Maherali *et al*., 2007; Wernig *et al*., 2007). The latter involves introducing four transcription factors (Oct-3/4, Sox2, c-*Myc*, and KLF4) into fibroblasts to generate induced pluripotent stem cells. This method is feasible in mice, but has not been tested in humans. A third approach is to use diplodized parthenogenetic human blastocysts to derive major histocompatibility complex (MHC)-matched pluripotent parthenogenetic human ESC lines (Revazova *et al*., 2007). This is equally promising and currently under investigation.

## A further note on the nature of the debate on human ESC research

The stem cell debate also contains a good measure of what may be considered hypocrisy: the use of surplus embryos in stem cell research is opposed by the current US administration because of concern about 'respecting human dignity and protecting human life', and yet the same administration appears unconcerned that its fraudulent *casus belli* has caused the loss of countless human lives in Iraq, including large numbers of civilians (Burnham *et al*., 2006). Moreover, while the use of surplus human blastocysts is vehemently opposed on moral grounds, international humanitarian laws and conventions are blatantly ignored (Amnesty International, 2007). On the home front, the government's budget proposals have consistently included cutbacks to critical social programmes such as the federal healthcare and welfare programmes for the poor. These actions and policies are decidedly disrespectful of human dignity and human life.

Worldwide, an unconscionable 30,000 children under the age of 5 years die every day as a result of armed conflicts and preventable or treatable diseases (The United Nations Children's Fund, 2005). Unlike human embryos, these children are human beings, although 'excluded and invisible' (The United Nations Children's Fund, 2006). In a 21st century where the United Nations has called for the world to 'recommit to its moral and legal responsibilities to children – one billion of them robbed of their childhood, living in poverty, in countries in conflict, in communities besieged by HIV/AIDS' (The United Nations Children's Fund, 2005) – the real moral outrage is the obstinate and unreasonable preoccupation of some with saving human blastocysts from destruction.

## Human ESC research in the context of human embryo research

The US scientific community would do well to remind everyone (and itself) that human ESC research must be considered in the larger context of human embryo research, the history of which in the USA is at once long and short, and profoundly disappointing. This history is extensively chronicled by RN Green (2001) in his book, *The Human Embryo Research Debates: Bioethics in the Vortex of Controversy*. In brief, after Steptoe and Edwards (1978) announced the birth of Louise Brown, the US Congress created an Ethics Advisory Board with the duty of recommending guidelines for federally funded research in IVF. Their report in May 1979 recommended the acceptance of research on human embryos but, due to tremendous opposition, mainly from religious groups, it simply stalled until the Board's charter expired. The result was a de-

**Table 1.** Unacceptable research as defined by the Human Embryo Research Panel in 1993.

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| Cloning by embryo splitting followed by transfer |
| Cloning by somatic cell nuclear transfer followed by transfer |
| Research beyond the onset of closure of neural tube |
| Fertilization of fetal oocytes with transfer |
| PGD for sex selection for non-medical reasons |
| Development of human–human or human–non-human chimaeras with or without transfer |
| Cross-species fertilization except for diagnostic tests |
| Transfer of parthenogenetically activated human eggs |
| Transfer of human embryos into non-human animals |
| Transfer of human embryos to induce extra-uterine pregnancy |

facto moratorium on federal funding of human embryo research that remained unchallenged for 14 years. In 1993, a Democratic-majority Congress passed a law nullifying the requirement for Ethics Advisory Board approval of federally funded research involving human embryos, which meant that the NIH was free to consider and fund research proposals.

At that point, a Human Embryo Research Panel was formed; the 19-member panel included prominent scientists, physicians, bioethicists, lawyers, and political scientists among others, and it was charged by Harold Varmus, then NIH Director, to provide advice to the Advisory Committee to the Director about embryo research. In September 1994, the Panel produced a report recommending that the NIH support a wide range of research on human embryos, including embryos that were 'created' for research purposes only. The Panel also defined 10 areas of 'unacceptable research', although according to Green, who was himself a panel member, these were not extensively debated. The 10 areas are shown in **Table 1**.

Interestingly, although it recommended against these areas of research, the Panel, with keen foresight, recognized the potential benefits of at least two of the above areas, namely, human–human or human–non-human chimaeras and induction of an extra-uterine pregnancy. The caveat, 'followed by transfer', that appears on several occasions in the list is also noteworthy, as it emphasizes the point that, unless the well-being of a recipient or a resulting child would be in jeopardy, none of these experiments *per se* is objectionable or should be subject to prohibition.

In December 1994, the Advisory Committee to the Director voted unanimously to accept the recommendations of the Panel, the final step in allowing the NIH to fund embryo research. However, on the same day, President Clinton issued a statement against the use of federal funds for the creation of human embryos for research purposes and directed that the NIH should not allocate any resources for such research. The remaining recommendations were also disregarded in August 1995, when Representative Jay Dicky introduced an amendment that would bar researchers who received federal funds from using the funds for projects involving human embryos. When this amendment was passed by Congress, all doors were closed to federal funding of human embryo research.

## Conclusion

A consideration of the Dicky amendment brings this commentary to its logical conclusion: the current debate on human ESC research is misguided. It is becoming increasingly clear that the federal government's position is unpopular and ultimately untenable. However, the problem at hand is not just the lack of funding for human ESC research; it is the systematic shunning, through predominantly faith-based political intervention, of a much wider and vital area of scientific inquiry – that of human embryo research. A rational discourse between scientists and the public would convey to the public and, in turn, to political leaders and law-makers that research involving human embryos does not betray any principle of morality. Research is fundamental to the understanding of human development and to progress in medicine; it is therefore a matter of public health. That human embryo research should be pursued with vigour is evident.

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