Article

An approach to the ethical donation of human embryos for harvest of stem cells

Dr Schwartz is a full-time stem cell biologist who, for the last 10 years, has been involved in the harvest of brain stem cells from patients who have died with neurogenetic disease. The research in his laboratory is directed towards understanding the factors influencing the behaviour of human brain stem cells derived from the normal and neurogenetically diseased brain. He is also interested in novel ways of deriving human embryonic stem cells and in deriving brain stem cells from these cells. Dr Schwartz conducts a human embryonic and brain stem-cell culture training course.

Dr Philip H Schwartz

Philip H Schwartz[1,3], Scott B Rae[2]
[1]National Human Neural Stem Cell Resource, Children's Hospital of Orange County Research Institute, 455 South Main Street, Orange, CA 928683874, USA; [2]Department of Philosophy, Talbot School of Theology, Biola University, La Mirada, CA, USA
[3]Correspondence: Tel: +1 714 5164310; Fax: +1 714 2894531; e-mail: pschwartz@choc.org

Abstract

This paper considers embryo grading within a given infertility treatment and suggests an ethical approach to embryo donation for embryonic stem cell harvest. It is concluded that ethical considerations regarding human embryos do not necessarily preclude the use of certain embryos for biomedical research or transplantation. The argument is based on the following rationale: all embryos are not physiologically equal, some low-grade embryos will never be chosen for implantation, cells from low-grade embryos may be donated for transplantation or research, and embryonic stem cells can be harvested from low-grade embryos. This argument bears special importance at this time as embryos created by IVF are still the only source of embryonic stem cells, given the current controversy surrounding published studies of human somatic cell nuclear transfer.

Keywords: *blastocyst, embryo transfer, human embryonic stem cells, IVF, pregnancy*

Introduction

Few advances in science have generated as much controversy as has the discovery that embryonic stem cells (ESC) can be derived from the human pre-implantation embryo (Reichhardt *et al*., 2004), generated by IVF. The potential of these cells to replace dead or damaged cells in any tissue of the body may herald the advent of a new field of medicine that can deliver cures for diseases now thought to be incurable. The controversy lies in the technique required to harvest these cells: destruction of the human embryo (Thomson *et al*., 1998). The debate cannot easily be settled because the crux of the controversy is not a scientific definition of human life, which begins at syngamy, but rather a philosophical definition, which is derived from one's world view and, in many cases, is religiously grounded. A substantial segment of the population holds that the destruction of viable human embryos for the harvest of human embryonic stem cells is morally repugnant, and some of these same individuals will refuse therapy based on this technology (Meyer, 2000; Ohara, 2003). This is why there is such intractable debate on this subject in the culture at large, though perhaps not reflected in the scientific community. Therefore, efforts by the biomedical and bioethics communities to seek new ways to develop this technology (Holden and Vogel, 2004) so that it may be more widely acceptable should be viewed as an important, indeed mandated, service to a significant segment of the population for whom these therapies are being developed, rather than as a distraction to the research efforts currently underway (Melton *et al*., 2004). The goal in this paper is to present an approach that may appeal to the segment of the population that views embryos as persons, a position for which a plausible argument can be made.

Recent research in the field has focused on alternate sources for embryonic stem cells. For example, as summarized by the President's Council on Bioethics, altered nuclear transfer, embryo biopsy and oocyte assisted reprogramming have been proposed as methods to create modified embryos, to harvest stem cells without harming embryos, or to bypass creating embryos at all, respectively (Editorial, 2005). Even though they will

probably be ethically more acceptable, there are still significant ethical questions remaining with each of these approaches. In addition, though there may be promise in each method, they are all still some time away from yielding usable stem cells and may involve high developmental costs. While there is, as yet, no experimental evidence supporting the feasibility of altered nuclear transfer or oocyte assisted reprogramming, however, the blastomere approach has been validated with mouse cells (Delhaise *et al*., 1996; Chung *et al*., 2005).

The goal of another technique, somatic cell nuclear transfer (SCNT), is not only to provide a source of ESC outside the confines of IVF but also to provide a source of cells that are immunologically matched to the patient for whom they are intended (Lanza *et al*., 2002). Unlike the other three techniques, there is ample experimental evidence in non-human species that this technique is feasible (Simerly *et al*., 2004). Although the technique reportedly has been successful with human material (Hwang *et al*., 2004, 2005), recent allegations of ethical improprieties and scientific fraud have called into question the apparent success of the technique (Cyranoski, 2005; Holden, 2005; Vogel, 2005a,b). Indeed, the two papers describing human SCNT (Hwang *et al*., 2004, 2005) have been withdrawn. Thus, one is still left with the products of IVF as the only source of ESC. As a result, this study considers the option of harvesting stem cells from low-grade embryos. It is suggested that, due to their morphological flaws and resulting high likelihood of miscarrying, these embryos can be acceptable sources of human embryonic stem cells, analogous to harvesting organs from non-heart beating or 'brain dead' donors. This case is made below.

All embryos are not physiologically equal

In the IVF clinic, pre-implantation embryos are graded for implantation suitability by the embryologist and physician, using primarily morphological criteria that are based on a long history of empirical data (Boiso *et al*., 2002; Gardner and Sakkas, 2003). These criteria are increasingly becoming biologically based, in addition to morphologically based. Within the context of a given infertility treatment, some embryos are graded as acceptable for implantation while others are not. On morphological grounds, expanded blastocysts with an oval inner cell mass (ICM) and cohesive trophectoderm (TE) are preferentially selected for implantation. Selection from among suboptimal embryos is based on their deviations from optimal blastocysts, in order of increasing morphological abnormality: cytoplasmic fragments and necrosis in TE, unexpanded blastocoele, non-compact or small ICM, fragments in TE and ICM, up to 20% excluded blastomeres, necrotic TE and ICM, and more than 20% excluded cells from blastocysts. Birth rates decline by the same order. Those embryos that are graded as acceptable, therefore, may be implanted or may be cryopreserved for implantation at a later date. Those that are not graded as acceptable are usually allowed to die or may be implanted if there is no other choice (*vide infra*).

The important issue to consider here is that infertility treatment in an IVF clinic is exclusively done on a case-by-case basis (Boiso *et al*., 2002; Gardner and Sakkas, 2003). This means that for a given treatment the eggs harvested and fertilized are considered, for implantation purposes, as a single group independent of the products of any other infertility treatment. As a result of fertility hormone treatment, 0–20 (or more) eggs may be harvested. Usually, all the eggs are fertilized and the resulting embryos are then graded. Ordinarily (and much more commonly), one or two high-grade embryos are implanted while the remaining are frozen and stored for possible later implantation. Freezing of higher-grade embryos and implanting fresh lower grade embryos also occurs. The range of numbers and grades of embryos across cases may be quite broad but, since these are considered on a case-by-case basis, the numbers and grades of embryos for a particular case have no relation to those for any other case. That is, a case of many high-grade embryos has no effect on the clinical approach to or outcome of a case with few low-grade embryos.

Most, if not all, low-grade embryos will never be chosen for implantation

Although technical advances have made it possible to implant low-grade embryos, their implantation rate is low, their miscarriage rate is high, and implantation of such embryos is reserved for cases in which no other higher-grade embryos are available (Boiso *et al*., 2002; Gardner and Sakkas, 2003). Although low-grade embryos may be implanted in some cases, it would be contrary to established clinical practice to implant a low-grade embryo when a suitable high-grade embryo is available. The maternal burden for low-grade embryos to survive and flourish is significantly higher than that for high-grade embryos. That is, subjecting a mother to a higher risk of miscarriage may be unwise from the perspective of the woman carrying the child. Indeed, it might be considered unethical to allow a mother to attempt to carry a low-grade embryo under these circumstances, as it would result in the abandonment of high-grade embryos in favour of low-grade embryos. Similarly, given the high likelihood of miscarriage, it would be unethical to donate low-grade embryos to other infertile couples who are seeking them, given that the number of high-grade embryos available for 'adoption' far outweighs the demand (Katz, 2003).

An important consideration here, given the discussion above, is that the decision as to whether or not to implant a low-grade embryo is also made on a case-by-case basis. Consider, for example, a case wherein 20 eggs have been harvested and fertilized and 10 embryos are considered high-grade, five medium-grade, and five low-grade. In this particular case, the couple decides to have a maximum of two children, thus two high-grade embryos are implanted, giving rise to a successful pregnancy with twins. Therefore, eight high-grade, five medium-grade, and five low-grade embryos remain. Consider further a second case wherein two eggs are harvested and fertilized and two low-grade embryos result. The couple desires to have one child, thus both low-grade embryos are implanted but no successful pregnancy results. In the former case, many embryos of different grades are produced but only the high-grade embryos are implanted. In the latter, only a very few low-grade embryos are produced and all are implanted. Even if the couple in the former case allowed the couple in the latter case the opportunity to 'adopt' some of their excess embryos, the physician for the couple in the latter case would choose only the

high-grade, not the low-grade, embryos. What is demonstrated here is that although low-grade embryos between cases may be physiologically equivalent, they are not necessarily equivalent in terms of their clinical potential. That is, the only reason low-grade embryos would even be considered for implantation is that they are the only option available to a couple who has spent thousands of dollars in IVF to this point. Given their options either to start the IVF process over again or to walk away, it is not unreasonable for them to attempt to implant these embryos, even though they are aware of the very high likelihood of miscarriage. If they had the option to implant high-grade embryos, they would certainly do so and it would be unethical to insist that the low-grade embryos be implanted due to their morphological flaws and high probability of miscarriage. Thus, the important consideration here is not solely whether or not an embryo is of low-quality but the quality of that embryo in the context of a given infertility treatment.

One approach to this, recently legislated by the Italian government (Boggio, 2005), obviates these considerations: a maximum of three eggs may be fertilized and all three must be implanted. This has the effect of eliminating the possibility of supernumerary embryos, and of maximizing the probability of implanting abnormal embryos and of multiple pregnancy.

Cells from low-grade embryos may be donated for transplantation or research

The pre-implantation embryos that have been graded as unacceptable for implantation in the case where suitable high-grade embryos exist, can therefore be donated for research or transplantation purposes under current guidelines for tissue or organ donation. There clearly must be a distinction between supernumerary embryos of implantation quality, that is, embryos of high quality that are in excess of implantation needs, and supernumerary embryos of poor quality that will never be chosen because of the availability of suitable high-grade embryos. Therefore, it is only the low-grade embryos present in a case where suitable high-grade embryos exist that might qualify for stem cell harvest.

Thus, couples are not under obligation to implant low-grade embryos, given their high likelihood of miscarrying. Further, it is suggested that it would be unethical to allow donation of low-grade embryos, again due to their high odds of miscarrying. With couples that have embryos suitable for implantation available, it would raise ethical concerns to suggest that they have an obligation to implant all low-grade embryos. There does not seem to be any realistic alternative to the disposition of low-grade embryos for couples undergoing IVF, unless said couples wish to freeze their embryos indefinitely (a situation that is illegal in some countries). In the absence of alternatives, it is proposed that harvesting stem cells from such embryos is acceptable.

Although not strictly analogous, as no strictly comparable situation exists, the non-heart beating organ donor (NHBD) may provide one way of viewing this, even though the NHBD is a controversial situation in itself (Herdman *et al*., 1998; Papalois *et al*., 2004). For a NHBD, life-sustaining technologies (LST) are generally removed in the operating room, allowing organ harvest to be done expeditiously after the declaration of death, usually within 5 min of removal of LST. What makes NHBD feasible is the ability to sustain a patient's vital functions artificially after the declaration of death, parallel to the more common organ harvest from a brain-dead patient (Truog and Robinson, 2003). Thus, a terminally ill patient with a poor prognosis being sustained on LST is a candidate for non-heart beating organ donation. It is suggested that low-grade embryos, with their very low prospects of implanting successfully, resemble the NHBD. Embryos awaiting implantation are sustained in a medium designed to enable full embryonic growth and development. When stem cells are harvested, the embryo is put into another medium (Thomson *et al*., 1998), one not suitable for full embryonic development but appropriate for continued metabolic function and thus, for stem cell harvest. It is suggested that this is analogous to removal of LST from a NHBD prior to reinstitution of support of vital functions necessary for successful organ harvest. That is, that taking embryos out of the IVF medium is analogous to removing LST. A major difference is that the NHBD is declared legally dead prior to organ donation, normally within a few minutes after LST are withdrawn. Embryos from which stem cells will be harvested have metabolic activity sustained in a different medium, though they are not declared dead as in the case of the NHBD. Although it can be argued that another important difference between the NHBD and the embryos is that the former can consent while the latter cannot, this only applies to patients that can legally give consent and does not apply to the very young or mentally incapacitated patient for whom consent must be given by a legal guardian (i.e. the exact situation that exists for the embryos).

A parallel may also be made with the situation wherein organs are donated from 'brain-dead' individuals. In this case, a medical determination (with legal underpinnings) has been made that the medical condition of the patient in question precludes or is incompatible with any quality of life, in this case a loss of any brain function. The loss of brain function is permanent and complete, with the result that the cardiopulmonary function of the patient is entirely dependent on medical, mechanical, and pharmacological intervention. Thus, the patient is declared 'brain dead'. Current ethical and legal considerations allow for harvest of organs (i.e. heart, lungs, kidneys) for transplant while the patient's cardiopulmonary system is still functioning (albeit artificially). In this situation, consent is given by the legal guardian. This is the only medical condition wherein this is allowed, the reason being that there is no hope of recovery of neurological function. These considerations may also apply to the poor quality embryos. That is, due to the clinical considerations surrounding implantation, the low quality embryos' condition precludes them from attaining any 'quality of life'. As no nervous system exists, no 'withdrawal of life support' may be necessary before stem cell harvest is performed.

The authors are aware that the use of the parallel to the brain dead organ donor above is premised on view of brain death that is still under debate among clinicians and bioethicists. The dead donor rule, in which organ donors must be clinically dead in order to ethically donate vital organs, governs organ donation, and is the standard reflected in the law. The concept of brain death was constructed decades ago in order to enable clinicians to harvest

organs from the severely neurologically compromised, while at the same time, adhering to the dead donor rule. The embryo unacceptable for implantation is analogous to the brain dead patient, technically still alive clinically. Under such a view, the patient who meets brain death criteria has all the characteristics of a living person except for consciousness. Organ donation is ethically justified not because the patient is dead, but because they are severely and permanently neurologically compromised. By analogy, ESC harvest is justified not because the embryo is dead but because the embryo has no possibility for development by virtue of not being implanted due to its morphological flaws. It is acknowledged that the embryo at this stage has metabolic activity, but due to its low-grade status has a high likelihood of miscarriage.

This view differs from another recent attempt to justify some human ESC harvest. The view of Landry and Zucker (2004) that some non-viable embryos are actually physically dead, as measured by irreversible cessation of cell division rather than the death of all cells, differs slightly from ours. There are no ethical issues with this approach, but there are questions about the ability to harvest stem cells successfully from only such embryos, although Cowan *et al*. (2004) suggest that it may be possible.

ESC can be harvested from low-grade embryos

Although it may seem counterintuitive that embryos graded as unacceptable for implantation would still be suitable for stem cell harvest, studies have shown this to be true (Cowan *et al*., 2004). Although Cowan *et al*. (2004) state that many of the embryos were of such poor quality that they did not develop or divide, cell lines were produced from three of these low-grade blastocysts. An additional four cell lines were derived from embryos of intermediate quality. These data show that over 40% of the new lines established by (Cowan *et al*., 2004) were established from embryos that, using standard IVF criteria, may not ever have been chosen for implantation.

At this point, it is difficult to assert whether or not ESC harvested from high-grade versus low-grade embryos would be of equal quality with regard to their potential research or clinical applications. The technique of IVF itself, which provides the starting material for the derivation of ESC, often produces genetically abnormal embryos (Niemitz and Feinberg, 2004) and ESC themselves are notoriously genetically unstable (Draper *et al*., 2004). There is currently no way of knowing whether ESC are completely genetically normal and would be safe to use in stem-cell therapy. Indeed, long-term safety studies may well take decades to complete. Moreover, there is emerging data that suggest that each ESC line possesses a differing capability for differentiation towards a specific lineage and that this capability varies with passage number (Maitra *et al*., 2005).

It should be pointed out that utilization of the principles espoused here implies that predominately prospective strategies for obtaining embryos for stem cell harvest must be used; embryos currently in storage in infertility clinics may not meet the criteria so far set forth. That is, consenting procedures should be established in IVF clinics that allow, prospectively, couples seeking IVF implantation to donate their low-grade embryos for stem cell harvest. However, the criteria should be further delineated such that they formally take into consideration the number of embryos created for a given infertility treatment, the grade distribution of those embryos, and the number of children desired by the couple under consideration. These consenting procedures should, by necessity, also preclude conflicts of interest on the part of the embryologist or IVF physician. In addition, although morphological criteria are still the most commonly used predictors of embryo quality, recent research indicates that molecular criteria might be a useful supplement to morphological criteria (Gardner and Sakkas, 2003; Borini *et al*., 2005; Wells *et al*., 2005). The arguments used can easily be applied to any criteria that are used to evaluate embryo viability and implantation potential.

There may be another class of embryo that fits into the same criteria, though by a completely different consideration. These are the embryos deemed as unsuitable for implantation because of genetic abnormalities detected by the technique of pre-implantation genetic diagnosis (PGD) (Boiso *et al*., 2002; Edwards, 2005). In the IVF clinic, the problem of producing embryos with genetic abnormalities is being addressed using the technique of PGD in certain at-risk individuals. Currently, at-risk individuals are defined as high maternal age egg donors and those in whom there is already a familial history of genetic defects. With PGD, one to three blastomeres are removed from the embryo at the 8–12-cell cleavage stage. (The resulting embryo can develop normally after removal of the blastomeres.) The removed blastomere(s) is then genetically evaluated using polymerase chain reaction, fluorescence in-situ hybridization, or comparative genomic hybridization. Only blastocysts from which the corresponding blastomeres have been shown to be normal by PGD are implanted. Application of PGD to IVF has significantly increased implantation rates, reduced spontaneous abortions, and reduced chromosomally abnormal conceptions (Gianaroli *et al*., 2005; Munné *et al*., 2005a, 2006).

The issue with PGD in the current context is the ethical status of those embryos shown by PGD to have a genetic abnormality that is incompatible with life. These embryos, like the poor-grade embryos described above, will never be implanted because they have genetic anomalies that will prevent them from surviving the gestational period. These embryos would be analogous to persons who are candidates for non-heart beating organ donation, or even brain dead organ donors. It can be argued that since it has been medically determined that these embryos have a lethal genetic defect, it would be ethical to donate cells from those embryos for research (but not transplantation). Recent studies have suggested that although such embryos might be chromosomally abnormal, there tends to be a degree of mosaicism that develops that allows the possibility of establishing normal ESC sub-clones from ESC harvested from these embryos (Munné *et al*., 2005b).

Conclusion

A plausible way to break the stem cell logjam when it comes to the ethical issues concerning the source of the stem cells is suggested. Thus, some embryonic stem cell harvest would be considered ethically acceptable, using embryos that would never be implanted due to some intrinsic defect and concurrent set of clinical conditions. For the sizeable portion of the general population that opposes embryonic stem cell research, this may

not be a satisfactory approach. This perspective is advanced in the hope that it could be viewed as an acceptable public policy compromise that would prevent destruction of high-grade embryos in the future.

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