Human Embryonic Stem Cells: Ethics, Myths and Realities

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Abstract: *Human embryonic stem (ES) cells can be obtained by the In Vitro Fertilisation (IVF) procedure. Their interest derives from the fact that they are capable of developing into virtually any cell of the body, given appropriate conditions. They can also be derived by removing the nucleus from a cell of a person's body and placing it inside an ovum (egg cell) provided by a donor, and from which the nucleus has been removed. This nuclear transfer procedure has become known as "therapeutic cloning." If the manufactured embryo were to be implanted into a uterus it would be called "reproductive cloning." Obviously, these approaches to deriving ES cells involve destruction of the embryo, and it is here that major ethical issues arise, which will be discussed. It must be stressed that research in "therapeutic cloning" is at such an early stage that every step is fraught with difficulties.*

Key Words: embryonic stem cells; therapeutic cloning; somatic cell nuclear transfer; IVF; bioethics; biomedical research – legislation; human embryo – legal status

What are Embryonic Stem Cells?

Human embryonic stem (ES) cells can be obtained by the In Vitro Fertilisation (IVF) procedure. Their interest derives from the fact that they are capable of developing into virtually any cell of the body, given appropriate conditions – they are "pluripotent." They can also be derived by removing the nucleus from a cell of a person's body and placing it inside an ovum (egg cell) provided by a donor, and from which the nucleus has been removed. This nuclear transfer procedure – Somatic Cell Nuclear Transfer (SCNT) – has become known as "therapeutic cloning," because the resulting cloned human embryo is almost an identical clonal replica of the human subject from whom the somatic cell nucleus was taken. Stem cells can be generated from this cloned embryo, and those cells used as the source of specialised cells which would not be rejected as foreign if they were to be used in the individual from whom they were derived.

If on the other hand the manufactured embryo were to be implanted into a uterus it would be called "reproductive cloning." It is this approach that was used to yield the now famous sheep, "Dolly." Human reproductive cloning is rejected entirely by scientists, as well as by politicians who have discussed it publicly, and is completely contraindicated for a number of reasons. Where legislation has been passed that permits therapeutic cloning, reproductive cloning has been unequivocally rejected.

Obviously, these approaches to deriving ES cells involve destruction of the embryo, and it is here that major ethical issues arise. These issues are relevant to legislation on this matter by the Governments of several countries, including Australia. They relate to concerns of a broad spectrum of the community, embracing virtually all the religions and those of no religion at all.

Most media attention is on embryonic stem cells, and the urgent pressure to use them in treatments. The media gloss over an important distinction regarding stem cell research. One form is embryonic stem cell research, which can only be conducted by using a developing embryo in a process that destroys it. The other form is adult stem cell research, which makes use of the evidence indicating that virtually all tissues of the body contain a number of stem cells that are "multipotent" – i.e. they can develop into several different types of adult cell.

Adult Stem Cells

For many years it has been known that the haemopoietic stem cell (HSC) is able to generate all the cell types of the blood and immune system, and this has been put to great therapeutic use. We know also that a primitive marrow stem cell (MSC) or blood vessel wall cells mobilised from marrow are able to repair heart muscle after damage from infarction. Such MSC's or vascular cells have been injected into immune-deficient rats in which a "heart attack" has been induced by tying off one of the blood vessels supplying part of the heart. This results in heart muscle death, but the injected bone marrow stem cells successfully integrated with the affected part of the heart and promoted blood vessel formation and healing.[1] In addition to the these discoveries, in the last year multipotent cells have been grown from umbilical cord vein blood and from cells taken from the lining layer of the nose.[2] These findings with adult stem cells provide every reason to give the strongest support to research seeking their eventual application to treatments of certain human diseases. Besides, the science of adult stem cells is moving at a fast pace, and there are now many examples of proof in experimental animals of the concept that adult stem cells can be used successfully in treatment, and clinical trials in human subjects are being undertaken,

Embryonic Stem Cells in Treatment

For all the rapid progress, there are many questions still, and much needs to be done in adult stem cell research. In the case of ES cells the problems besetting this work are so great that one has to question the pressure being applied that it is so urgently needed, that that work on HES cells is absolutely essential and urgent in order to discover new treatments for previously untreatable chronic diseases. The usual list consists of diabetes, Parkinson's Disease, Alzheimer's, muscular dystrophies, the replacement of dead heart muscle following heart attacks, of brain tissue following strokes, etc. For several of these conditions there are appropriate experimental models that can be studied in animals, but in no case have embryonic stem cells been shown in animal research to provide a cure that is sufficiently prolonged and free of complications to warrant human studies. This should be a minimum requirement if the urgency of work on human embryonic stem cells is to be accepted in the face of the ethical barrier.

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[1] Yoon et al, "Clonally Expanded Novel Multipotent Stem Cells from Human Bone Marrow Regenerate Myocardium after Myocardial Infarction," *Journal of Clinical Investigation* 115 (2005): 326-338; D. Orlic et al, "Mobilized Bone Marrow Cells Repair the Infarcted Heart, Improving Function and Survival," *Proceedings of the National Academy of Sciences USA* 98 (August 28, 2001): 10344-10349; A.A. Kocher et al, "Neovascularization of Ischemic Myocardium by Human Bone-Marrow-Derived Angioblasts Prevents Cardiomyocyte Apoptosis, Reduces Remodelling and Improves Cardiac Function," *Nature Medicine* 7 (2001): 412-423.

[2] W. Murrell et al, "Multipotent Stem Cells from Adult Olfactory Mucosa," *Developmental Dynamics* 233.2 (2005): 496-515; G. Kogler et al, "A New Human Somatic Stem Cell from Placental Cord Blood with Intrinsic Pluripotent Differentiation Potential," *Journal of Experimental Medicine* 200 (2004):123-135.

An example is provided by a study in which human ES cells that have been converted to dopamine-producing neuronal cells, have been injected into the brains of immune-deficient rats subjected to a chemically induced Parkinson's Disease. There were highly encouraging improvements in motility and behaviour of the animals, but 5 of 19 developed teratomata[3] – tumour formation being a major complication of ES cell transplantation. This ES cell approach for Parkinson's disease took a step further recently with experiments in monkeys in which a form of Parkinson's was chemically induced, and monkey ES cells transplanted. Some symptomatic improvement was noted, but only 1% of the transplanted cells survived, and the short observation time allowed no conclusion about the serious possibility of tumour formation.[4] This propensity to develop teratomas has been a feature of all the animal studies so far with ES cells - tumours being associated with ES cell transplantation into the pancreas for diabetes and into the heart for heart muscle damage. In the latter case also serious abnormalities of heart rhythm have occurred, a complication not encountered with adult stem cells used for the same purpose. With regard to spinal cord injury, when this has been experimentally induced in rodents, some partial improvement in mobility has been achieved both with adult and embryonic stem cells.[5] In each case a major factor in this improvement has been that the transplanted cells have influenced the formation of the protective myelin sheath around the nerve fibres. Progress with this condition is likely to be very slow, and dependent on understanding of the molecular events that control the ways in which the severed ends of the nerve fibres make contact. Much progress is being made in that area, and until now from animal experiments there is no good reason to suspect that ES cells offer advantage over a number of alternative cell therapy approaches. Alzheimer's is a global condition of the brain and its causes are unknown. The very nature of this disease makes it virtually impossible to conceive that any form of cell therapy could be helpful. And yet Alzheimer's disease appears almost invariably in the lists of possible curable diseases that are listed to the public.

At present there is no evidence from animal experimentation with either human or animal ES cells to justify even the most limited human trial of ES cells in therapy. Furthermore some of the proposed cures are highly unlikely, and others are on a very long time-frame. An essential requirement is that "proof of concept" be provided for the efficacy of ES cells in treatment of even one of the suggested targets – and the way to do this is to use animal models of disease. Any attempt so far has illustrated major difficulties confronting the embryonic stem cell approach. If there were no other possible way of finding stem cells capable of taking on functions other than those of their tissue of origin, then perhaps the pressure to undertake HES cell research would be very much greater.

Nuclear Transfer ("Therapeutic Cloning")

In aiming to prepare ES cells for use in treatments, from a purely scientific perspective it might make much more sense to use ES cells obtained by the somatic cell nuclear transfer

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[3] Borklund et al, "Embryonic Stem Cells Develop into Functional Dopaminergic Neurons after Transplantation in a Parkinson Rat Model," *Proceedings of the National Academy of Science USA* 99 (2002): 2344-2349.

[4] Y. Takagi et al, "Dopaminergic Neurons Generated from Monkey Embryonic Stem Cells Function in a Parkinsonian Primate Model," *Journal of Clinical Investigation* 115 (2005):102-109.

[5] Barnett et al, "Identification of a Human Olfactory Ensheathing Cell that Can Effect Transplant-Mediated Remyelination of Demyelinated CNS Axons," *Brain* 123 (2000): 1581-1588; J.W. McDonald et al, "Transplanted Embryonic Stem Cells Survive, Differentiate and Promote Recovery in Injured Rat Spinal Cord," *Nature Medicine* 12 (1999): 1410-1412.

process rather than unrelated ES cells (from IVF excess), that are subject to destruction by the immune system of the recipient. However to do this involves the deliberate cloning of human embryos in order to achieve whatever promise is offered by ES cell research. This method of producing ES cells derived by nuclear transfer involves removing the nucleus from a cell – it could be a muscle cell, or a skin cell – and placing it inside an ovum (egg cell) provided by a donor, and from which the nucleus has been removed. Although this has come to be called "therapeutic cloning ," this name is inappropriate and misleading. Human ES cells, obtained either from IVF embryos or through cloning, have never been use in treating human disease, and no trial could be planned based on present evidence. The practical difficulties associated with using cloning as a source of cells for treatment of individual patients are overwhelming, and the earlier enthusiasm for this approach has waned substantially. The currently favoured application of cells obtained by the nuclear transfer procedure is to use them in studying the mechanisms of specific diseases. For example, a clonal cell line could be established by transferring a somatic cell from a subject with a particular chronic and unsolved disease into an enucleated donor egg, developing cloned cells from the embryo, and studying their molecular controls during differentiation. The hope would be that this approach would provide clues to the mechanisms might lead to prevention or treatment. Thus the ethical question associated with the nuclear transfer approach to cloning has changed – rather than arguing for its use to provide for treatments, it would now be for research that might help in understanding of disease. The question then is: should this method be used to generate embryonic stem cells that might be used towards research into the treatment of a number of diseases?

The nuclear transfer method is not permitted in Australia, although permission under licence can be obtained by scientists in the UK. The birth of Dolly the sheep proved that this procedure was capable of generating an embryo, however Dolly was the only successful embryo produced out of 277 attempts. This reproductive cloning has been carried out with other species such as mice, cows and pigs. In all cases the method is highly inefficient, requiring a large number of eggs for each success, and is accompanied by a very high abnormality rate in the animals that have been born.[6] Although use of the nuclear transfer method to generate ES cells has been called therapeutic cloning, the name should best not be used. Such cells have never been used in clinical studies, and the practical difficulties associated with their preparation for therapeutic purposes (e.g. large donor ovum supply needed, risk of tumour development with transplantation) are at present insurmountable.

Ethical Issues and Legislation

There is widespread agreement that there is an ethical issue involved in experimenting on cells obtained from human embryos – sufficient agreement that the topic is one that receives major attention by Governments of a number of countries, including UK, USA, EU and Australia. As is always the case in medicine and related research, when undertaking a certain procedure requires that ethical barriers be surmounted, the more formidable that barrier, the greater must be the benefit of the proposed work. While it can be agreed that from the time of fertilisation the human embryo should be treated with respect because of what it can potentially become, it is the timing of application of that respect, and its level, that is argued. This issue presents serious ethical problems to a significant proportion of the population - to virtually all the Christian denominations and to people of the Jewish,

[6] I. Wilmut, "Are There Any Normal Cloned Mammals?" *Nature Medicine* 8 (2001):215.

Hindu and Muslim faiths. It is also a view shared by people of no religious proclamation. This ethical difficulty needs to be taken into consideration when formulating public policy. At present in Australia scientists can be licensed to undertake research on embryos that are maintained frozen in excess of requirements for IVF therapy, and made available with permission of the parents. That is our legislative *status quo* – it gives those interested in that research the opportunity to pursue it. The Government is currently considering whether to approve the production of embryos specifically for research, using the process often referred to as therapeutic cloning.

When the UK's House of Lords' Select Committee considered this question, it concluded with a recommendation that accorded with the British Government's approval of HES cell research, including the generation of embryos specifically for research purposes - something no other Government anywhere had done. It is interesting that their document contains a very clear statement that *"if there were no morally serious reasons for undertaking research on human embryos, then the mere possibility that the early embryo is a person would be sufficient reason not to do such research."* What compelling, morally serious reasons provided the House of Lords with the necessary imperative? The main stated reasons appeared to come from evidence given by people suffering from previously untreatable chronic diseases, who believed that cures would be provided from ES cell treatments.

In all branches of medicine it is mandatory that "proof of concept" is obtained through extensive preclinical experimentation in animal research before human studies are performed. Not in any of the diseases so commonly invoked, has there been such proof of concept obtained for the use of embryonic stem cells in treatment, and it is abundantly clear that much more animal experimentation must be carried out, even to establish in the first instance that any human clinical trial would have any chance of success. If its proponents could prove in even one experimental disease model that transplantation with ES cells results in a cure, that would go some distance towards meeting the House of Lords requirement of "morally serious reasons" for supporting ES cell research.

Just as there has been much learned about biology of development in studying mouse embryonic stem cells, it would be of great scientific interest to study developmental processes in human embryonic cells. The public arguments of scientists in favour of ES cells research have been changing significantly in the last year, moving away from cures for disease to the pursuit of knowledge, particularly by generating ES cells that provide for study of mechanisms of specific diseases. The pursuit of knowledge of nature and of disease from the study of human embryonic stem cells is an attractive scientific prospect. What has to be decided is whether doing this with human embryonic stem cells, purely on the basis of the pursuit of knowledge, provides sufficient good to overcome the major reservations held by a significant proportion of the community.

There is an ethical problem in dealing with human embryos in these ways and so there needs to be a very compelling case for working with them. A minimum requirement is that extensive animal experimentation establishes the validity of this approach, especially given the fact that adult stem cells have so far been far superior in performance in experimental and clinical therapeutics.

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The editorial board of AEJT acknowledges its thanks to Marcelle Mogg, the editor of Eureka Street for permission to reprint Dr Martin's article here.

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