The Irish Council for Bioethics

Comhairle Bitheitice na hÉireann

ETHICAL, SCIENTIFIC AND LEGAL ISSUES CONCERNING STEM CELL RESEARCH

OPINION

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Preface

Stem cell research presents considerable ethical challenges for scientists, policy makers and the wider community. In response to the debate prompted by European Union (EU) funding of embryonic stem cell research, the Irish Council for Bioethics appointed a rapporteur group in July 2006 to consider the scientific, ethical and legal questions emerging from this field of research.

Mindful of the diversity of ethical views held by individuals and members of the various communities living in Ireland, the Council was eager to consult stakeholders and the general public prior to deliberating on the subject. The rapporteurs met with several interested parties from the fields of law, science, medicine and theology, as well as prolife and patient advocacy groups. The Council then invited the Irish public, through local as well as national press and radio, to express its views on stem cell research by completing a questionnaire and submitting comments online or by post. An information leaflet, outlining the scientific basics of stem cell research, was made available to accompany the questionnaire. Over 2,000 individuals responded to this public consultation and the Council would like to express its gratitude for this effort, which greatly benefited its considerations.

The following report presents the considered consensus opinion of the Council on a wide range of ethical questions pertaining to the complex field of stem cell research. It is the result of extensive deliberations and I would like to take this opportunity to sincerely thank the rapporteurs and members of the Council who gave generously of their time and expertise, and the Council's professional staff, for their steady commitment to the Council's work programme.

The Council hopes its recommendations will be carefully considered and that this report will stimulate debate and discussion of the ethical implications of stem cell research for Ireland.

Dr. Dolores Dooley

Chairperson
Irish Council for Bioethics

Foreword

Recent developments in both adult and embryonic stem cell research offer the potential for understanding disease development and progression, for treating debilitating disease and injury, and for targeted drug development. Much of the ethical controversy relating to stem cells derives from the fact that, until very recently, the only way to obtain human pluripotent stem cell lines was to derive them from a human embryo by a process that necessarily destroyed that embryo.

One of the most widely discussed and most controversial questions in ethical and political debates of recent years is whether research on human embryos should be permitted and if so, what kind of research and for what purpose. Societal attitudes in relation to this question vary greatly, with some people fundamentally opposed to research involving nascent human life, while others take the view that research on human embryos offers a legitimate opportunity to garner new scientific and medical knowledge.

This Opinion document sets out in some detail the scientific basis of stem cell research. It considers the ethical issues in light of scientific advances and outlines the current legal situation in Ireland and internationally (supplementary material relating to regulation of stem cell research globally can be found in Appendix E). The strong emphasis placed on embryonic stem cell research in this document should not be interpreted as a reflection of the relative value the Council places on adult or embryonic stem cell research. The Council recognises and is supportive of the valuable research with adult stem cells that is currently being conducted in Ireland and elsewhere. Once such research is carried out in accordance with relevant legislation, scientific protocols and ethical guidelines, the ethical issues raised by the use of adult stem cells in research are comparable to those raised by the use of other human biological material in research. These issues have previously been addressed in detail in the Irish Council for Bioethics' report *Human Biological Material: Recommendations for Collection, Use and Storage in Research* (2005) and were, therefore, not covered in any depth in the current document. One aspect of adult stem cell research, which does raise specific ethical questions, relates to the collection and storage of umbilical cord stem cells. This issue has been considered in the Ethical Considerations section of the document.

In keeping with the Council's *modus operandi* since its establishment in 2002, a public consultation was undertaken prior to the drafting of this opinion document. It is important to make clear that the purpose of the consultation was to inform the deliberations of the Council, rather than serve as an opinion poll on the topic of stem cell research. The Council has made every attempt to reflect the differing views expressed and to weigh the associated arguments with diligence and objectivity. We are indebted to Dr. Patrick Flanagan who undertook primary responsibility for the analysis of the individual submissions, of which there were over 2,000. Thanks are also due to members of the public who participated in the consultation process. In addition, discussions with a number of interested parties in the area provided additional insights and were greatly valued and appreciated. (A list of submissions invited and received by the Council on the topic of stem cell research can be found in Appendices C and D respectively).

Following extensive research, careful consideration of stakeholder and public views, and much deliberation, the Irish Council for Bioethics presents this Opinion document, which represents the unanimous view of Council members on the issue of stem cell research.

We hope that this Opinion document, with its overview sections on the science, ethics and regulation of stem cell research, will serve as a source of clear, intelligible and useful information for both policy makers and the general public regarding the current state of this important research and of the debates that surround it.

The Council would also like to extend its gratitude to the members of the secretariat, Dr. Siobhán O'Sullivan, Ms. Emily de Grae, Mr. Paul Ivory and, in particular, Dr. Stephanie Dyke, who were instrumental in the compilation of this document.

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Professor Linda Hogan

Dr. Richard Hull

Rapporteur Group on Stem Cell Research
Members, Irish Council for Bioethics

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SCIENTIFIC ASPECTS OF STEM CELL RESEARCH

Introduction to Stem Cells

The human body is an elaborate mass of cells, each with a defined role and organised into tissues and organs. Every cell, whether in the liver, heart or brain, takes on its role by specialising into a particular cell type, with a characteristic shape and function, through a process called cell differentiation. Differentiation begins early in embryonic development and eventually leads to over 200 diverse cell types, whose orchestrated activity form the human body.

The idea of "stem cells", immature cells from which all specialised cell types derive, emerged in the late nineteenth century in response to fundamental questions in embryology, such as the origin of the blood system.[1] However, due to the limitations of the experimental methods available at the time, stem cells remained largely hypothetical until research on survivors of the 1945 nuclear bombings was carried out and the term re-emerged to describe cellular regeneration mechanisms found to exist throughout the body.

Studies of the renewal of blood cells, in particular, showed that a special type of cell—referred to as a stem cell—was capable of regenerating several types of specialised cells. Red blood cells, for example, have a short life span of about four months and must be replaced regularly during an individual's lifetime. This regeneration is guaranteed by stem cells residing in the bone marrow, which can differentiate into any one of the various types of blood cells, including red blood cells.

Stem cells constantly renew their stock so as to be able to replenish dead and damaged cells whenever needed. Hundreds of billions of the cells that constitute the adult body can no longer divide and must be replaced when they die and disappear. Every second, twenty million cells of our body divide to keep the number of stem cells and specialised cells needed for the body's function constant. Maintaining the number of red blood cells alone requires two million divisions per second.

Definitive evidence of the existence of blood stem cells was provided in the 1960s.[2,3,4] However, scientists are still trying to understand the main characteristics of these cells: what allows them to divide so readily, in contrast with most cell types, which, like red blood cells, have a limited lifespan; and how stem cells are able to differentiate into specialised cell types.

1 Ramalho-Santos M and Willenbring H (2007) On the Origin of the Term "Stem Cell". *Cell Stem Cell* 1(1): 35–38.

2 Becker AJ, McCulloch EA and Till JE (1963) Cytological Demonstration of the Clonal Nature of Spleen Colonies Derived from Transplanted Mouse Marrow Cells. *Nature* 197(4866): 452–454.

3 Till JE and McCulloch EA (1961) A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells. *Radiat Res* 14(2): 213–222.

4 Till JE, McCulloch EA and Siminovitch L (1964) A Stochastic Model of Stem Cell Proliferation Based on the Growth of Spleen Colony-Forming Cells. *PNAS* 51(1): 29–36.

Stem cells have generated a considerable amount of scientific and medical interest. Studying their behaviour will advance our knowledge of basic mechanisms of cell biology, such as cell differentiation and renewal, and of embryonic development. Many serious medical conditions, such as cancer and birth defects, are caused by problems with these fundamental processes. Stem cell research, by increasing our understanding of normal cell development, may allow us to understand, and possibly correct, the errors that lead to such medical conditions.

Due to their renewal and regenerative potential, stem cells also hold great promise for the treatment of diseases in which cells and tissues are diseased or damaged. This is the case in conditions such as Parkinson's and Alzheimer's diseases, stroke and heart disease, diabetes and arthritis. Stem cell therapy, also referred to as cell replacement therapy, would involve using differentiated stem cells to replace the patient's deficient cells (see Figure 1).

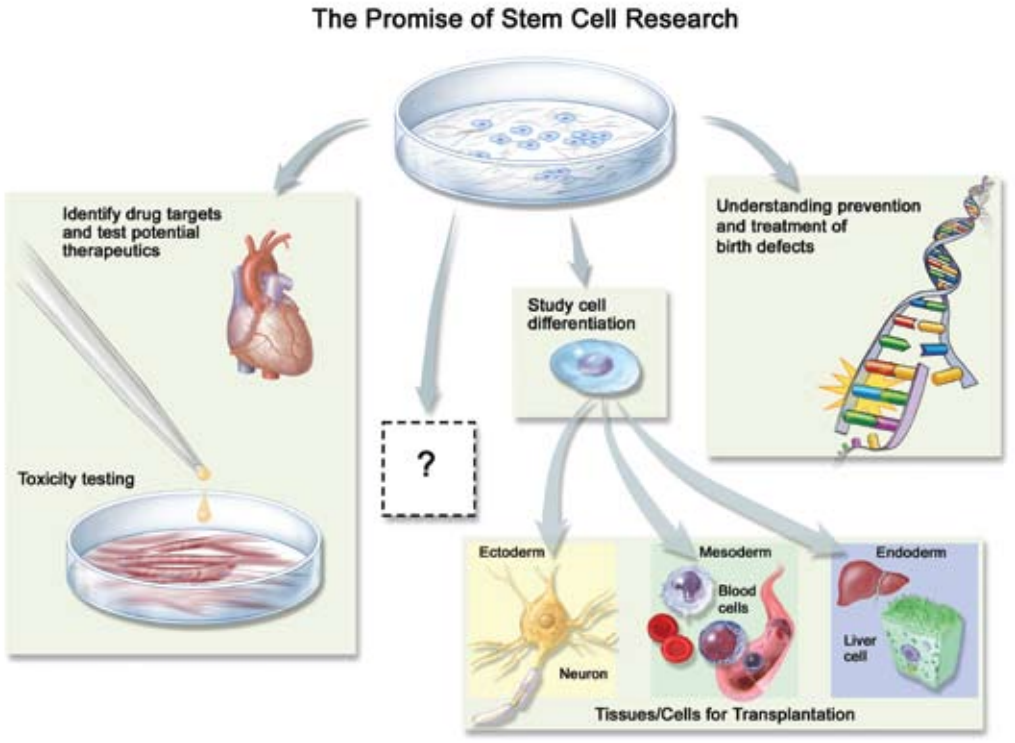

Figure 1. Potential applications of stem cell research

Stem Cell Lines

Due to their ability to multiply relatively easily, stem cells can be grown for long periods of time in the laboratory. Stem cells isolated from an organism and transferred to *in vitro*[5] culture are referred to as a stem cell line once their growth is regular and stable. Stem cell lines are generally grown in flasks and in incubators, which simulate the temperature, atmosphere and other elements of the natural environment of the tissue or organ from which the cells were derived.

Stem cell lines are particularly valuable as a research tool because they allow scientists to experiment with the cells to try and figure out how they work. It is possible, for example, to make stem cells differentiate into particular specialised cell types by adding certain molecules to the *in vitro* culture. Furthermore, if stem cell research eventually leads to therapies, large numbers of cells will be needed for treatments and they will most likely need to be expanded in culture before they can be transplanted into a patient. Since stem cells retain their capacity for differentiation after expansion *in vitro,* they can also provide a continuous supply of stem or specialised cells for basic research, disease modelling and drug testing.

Establishing stem cells as stable cell lines is an important step towards developing their promise and the techniques to do so are under active investigation. Certain types of stem cells have been easier to culture *in vitro* than others. Similarly, stem cells from certain species and even from particular genetic strains, are more readily established as cell lines. This highlights the complexity of stem cell biology and the current uncertainties concerning many of their properties.

Classification of Stem Cells

Stem cells are found in different locations throughout the body and are present from just after the fertilisation of an egg until the death of the organism. Stem cells are most commonly defined by the stage of development of the organism from which they are derived and scientists typically refer to work with embryonic, foetal and adult stem cells, depending on the source of these cells.

Stem cells have also been classified into three main categories according to their ability to differentiate into specialised cell types. They are said to be totipotent, pluripotent or multipotent, depending on how many cell types they can give rise to. Some stem cells are able to develop into an entire organism and are, therefore, referred to as totipotent. Those referred to as pluripotent are able to differentiate into all of the specialised cell types of the body but cannot generate an entire organism on their own. Finally, multipotent stem cells can only differentiate into a particular subset of specialised cell types.

The following sections of this document will review the main types of stem cells, notably, embryonic and adult stem cells.

5 *In vitro* literally means “in glass” and refers to the growth of cells in the laboratory in flasks and dishes.

Embryonic Stem Cells

Embryonic Development and Stem Cells

The process of fertilisation begins when a sperm cell reaches its female counterpart (an oocyte, or egg) and ends with the fusion of the paternal and maternal DNA (deoxyribonucleic acid) provided by these cells (23 chromosomes from each cell combine to form the full complement of the human genome). Fertilisation creates a single cell, called the zygote, which will normally proceed through the successive stages of embryogenesis as it develops into a foetus. Embryogenesis spans from the end of fertilisation (zygote stage) until the end of the eighth week of development, after which the developing human is referred to as a foetus.

The zygote begins embryogenesis with a series of cell divisions: it divides into two identical cells, which then divide to give four cells and so on (see Figure 2). These cells of the early embryo are totipotent embryonic stem cells and have the potential to develop into the hundreds of different cell types that make up the human body, as well as into those that form the structures that will support embryonic development, such as the placenta. If the group of cells splits apart at this stage, identical twins or triplets, *etc.* begin to develop. Four days after fertilisation, the embryo has become a solid ball of 16–32 cells called the morula. Over the next day, the morula develops into a hollow, fluid filled structure called the blastocyst. The embryo will now develop from a specific cluster of blastocyst cells referred to as the inner cell mass, embryonic disc, or embryoblast. These cells are pluripotent embryonic stem cells and will give rise to all of the different types of cells of the developing embryo. The rest of the blastocyst's cells will form the structures needed to support the embryo's development, *e.g.* the placenta and amniotic membranes. Embryonic stem cells can, therefore, be either totipotent or pluripotent, depending on the stage of development of the embryo from which they are isolated.

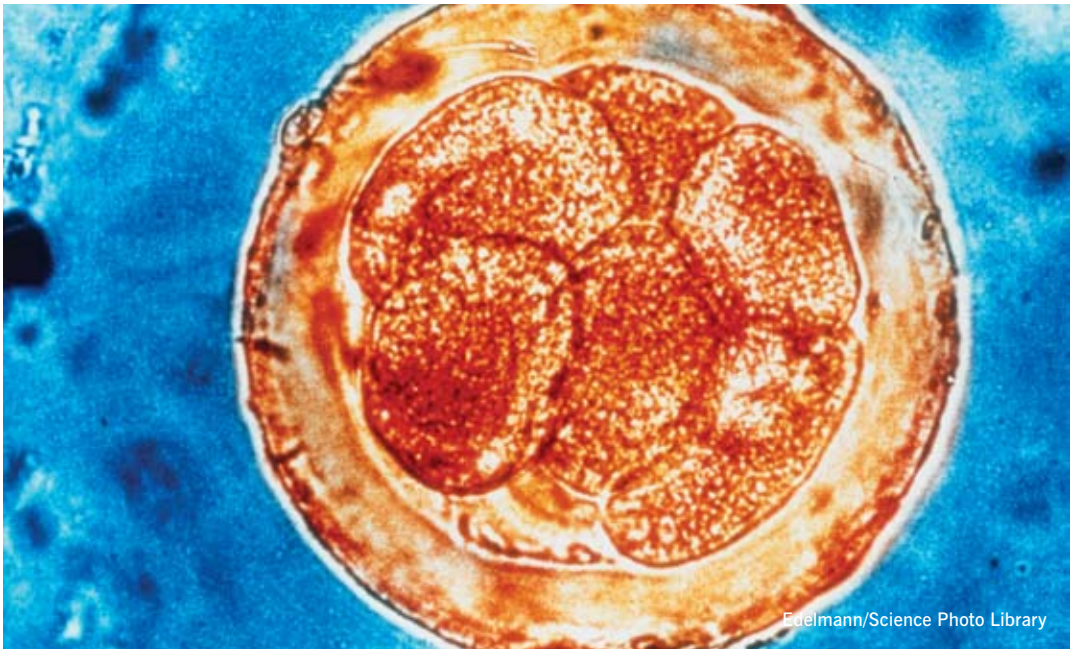

Figure 2. Human embryo at the eight cell stage

As the embryo develops from a zygote to a blastocyst it has, in the normal course of events, been travelling down a fallopian tube and into the mother's uterus. Once the blastocyst reaches the uterus (about five-to-six days after fertilisation), it begins to attach to the lining of the uterus. This process is referred to as implantation and should be complete by day 12[6] (usually day eight-to-ten).[7] Implantation connects the embryo to the maternal blood supply, allowing it to continue its development and establishing pregnancy.

At the beginning of the second week of development, the cells of the inner cell mass separate into distinct layers that will generate specific cell types in the developing embryo (now referred to as a gastrula). All of the cells have the same DNA, however, they begin to express different genes and will eventually form different tissues and organs. Until this process of gastrulation begins, twinning is possible. The primitive streak of the embryo forms as gastrulation continues (around day 14). This structure orients the early embryo, defining its head and tail, and can be described as the precursor of the embryo's vertebral column. As gastrulation proceeds, embryonic stem cells gradually lose their pluripotency.

Embryonic Stem Cell Research

Pluripotent embryonic stem cells were first isolated from the inner cell mass of mouse blastocysts in 1981.[8,9] These cells gave rise to cell lines that were capable of maintaining themselves for an unlimited time *in vitro*, a property that is normally limited to cancer cells. This "immortality" has not yet been seen in stem cell lines established from older embryos, foetuses and adult tissue.

In 1995, scientists isolated embryonic stem cells from a non human primate—the rhesus monkey—at the Wisconsin National Primate Research Centre in the United States (US). In 1998, the same group published an article detailing how human embryonic stem cells had been obtained and established as a cell line.[10] The researchers perfected a biochemical environment in which the stem cells would grow and divide but remain in their immature, "uncommitted" state. Only upon removing those biochemical controls did the cells begin to specialise. These human embryonic stem cells have so far been shown to successfully differentiate into neurons, glia (brain cells), hepatocytes (liver cells), muscle and various epithelia (*e.g.* skin). This achievement represented an incredible technical breakthrough for stem cell research. The stem cells were extracted from an embryo produced by *in vitro* fertilisation (IVF) and donated by a couple that was receiving infertility treatment. Around the same time, John Gearhart from John Hopkins University, Baltimore, obtained human embryonic like stem cells from germ cells extracted from aborted foetuses.[11] Both research groups spread the stem cells on a "feeder" layer of mouse cells to produce stable cell lines.

6 Day X refers to X days after fertilisation.

7 Wilcox AJ, Baird DD and Weinberg CR (1999) Time of Implantation of the Conceptus and Loss of Pregnancy. *N Engl J Med* 340(23): 1796–1799.

8 Evans MJ and Kaufman MH (1981) Establishment in culture of pluripotential cells from mouse embryos. *Nature* 292(5819): 154–156.

9 Martin GR (1981) Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *PNAS* 78(12): 7634–7638.

10 Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS and Jones JM (1998) Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* 282(5391): 1145–1147.

11 Gearhart J (1998) New Potential for Human Embryonic Stem Cells. *Science* 282(5391): 1061–1062.

Applications of Embryonic Stem Cells in Research

Stem cells hold particular promise for cell replacement therapy, which is the treatment of disorders characterised by diseased or damaged cells by transplanting functional cells derived from stem cells to reconstitute the tissue or organ.

Before new treatments can be tested in clinical trials, they must be evaluated in animal models of the human disease. Although they are not definitive predictors of what will occur in human patients, animal experiments provide an initial assessment of the value of a therapy, which is essential for it to be considered for clinical trials. Thus far, the embryonic stem cell research carried out in animals indicates that these cells hold considerable therapeutic promise for the treatment of neurological, heart, liver, muscle, bone and cartilage disorders, as well as for cancer therapy and the treatment of immune disease.[12]

Parkinson's disease is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech. The progression of the disease is linked to a loss of particular brain neurons that normally produce the neurotransmitter dopamine. Human embryonic stem cells have successfully been differentiated into dopamine producing neurons, which may be capable of replacing those that are lacking in diseased brains. However, in a recent study using rat models of Parkinson's disease, these cells did not lead to a reversal of the motor deficits.[13]

Embryonic stem cell therapy for the treatment of spinal cord injury is actively being developed by the US company Geron Corporation. In rat models of the injury, differentiated human embryonic stem cells not only repaired the nerves at the site of the injury,[14] they also produced factors that are known to expand and improve the survival of neuronal circuitry in the spinal cord.[15] The first clinical trial of an embryonic stem cell based treatment is planned for mid 2008. Geron plan to implant oligodendrocytes derived from embryonic stem cells in patients with spinal cord injuries.

Research groups in France, Spain, Israel and the US are currently working on making insulin producing pancreatic cells from embryonic stem cells, to replace those that are dysfunctional in diabetes patients.[16]

12 Mimeault M and Batra SK (2006) Concise Review: Recent Advances on the Significance of Stem Cells in Tissue Regeneration and Cancer Therapies. *Stem Cells* 24(11): 2319–2345.

13 Brederlau A, Correia AS, Anisimov SV, Elmi M, Paul G, Roybon L, *et al.* (2006) Transplantation of Human Embryonic Stem Cell-Derived Cells to a Rat Model of Parkinson's Disease: Effect of In Vitro Differentiation on Graft Survival and Teratoma Formation. *Stem Cells* 24(6): 1433–1440.

14 Keirstead HS, Nistor G, Bernal G, Totoiu M, Cloutier F, Sharp K and Steward O (2005) Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cell Transplants Remyelinate and Restore Locomotion after Spinal Cord Injury. *J Neurosci* 25(19): 4694–4705.

15 Zhang YW, Denham J and Thies RS (2006) Oligodendrocyte Progenitor Cells Derived from Human Embryonic Stem Cells Express Neurotrophic Factors. *Stem Cells Dev* 15(6): 943–952.

16 Fagniez P-L (2006) *Cellules souches et choix éthiques. Rapport au Premier ministre.* Paris.

Scientists at the Roslin Institute in Scotland, where Dolly the cloned sheep was born, have recently developed standardised liver cells from human embryonic stem cells, which can be used to model human liver function.[17] As mentioned above, pharmaceutical development currently relies on animal models for the testing of therapies and drugs. A standardised and limitless supply of functional human liver cells may provide scientists with a better tool for testing the toxicity and efficacy of new drugs.

The shortage of donor organs for transplantation remains a major obstacle in the treatment of many medical conditions. Stem cell research holds potential for the generation of transplantable tissues and organs, to be "grown" from embryonic stem cells. Although still in a very early stage of development, research is directed towards expanding the concept of cell replacement therapy: from the use of living cells to restore, maintain or enhance tissue function, to the generation of entire new organs from stem cells. This approach has so far been successful in engineering kidneys and pancreases in animals.[18]

Multipotent (Non Embryonic) Stem Cells

Adult Stem Cells

The term "adult stem cell" is misleading because these stem cells are also found in babies, children and even in umbilical cord blood. Adult stem cells can be obtained from many parts of the body, including bone marrow, brain, blood, skin, eye, muscle, liver and hair. It is currently believed that they are likely to be present in most of the body's tissues and organs, even if they have not yet been found.[19] Their job is to replace and replenish cells that are continually lost to disease and everyday wear and tear. A good example of the type of tissue repair guaranteed by adult stem cells is the healing process of skin cuts and scrapes.

Adult stem cells have differentiated to some extent during the development of the organism from which they come and are, therefore, restricted in terms of the cell types they can differentiate into. For this reason, they have been termed "multipotent", meaning that they can generate several cell types but, typically, only those of the tissue or organ in which they are found. For example, blood forming adult stem cells in the bone marrow are able to generate the three different types of cell that make up the blood.

There is some evidence, however, that adult stem cells may actually be more flexible than this and may, given the right conditions, be able to differentiate into cell types of very different tissues and organs than those from which they originate (referred to as plasticity). Experiments published in 2002 by Catherine Verfaillie's research group at the University of Minnesota, demonstrated that adult

17 Hay DC, Zhao D, Ross A, Mandalam R, Lebkowski J and Cui W (2007) Direct Differentiation of Human Embryonic Stem Cells to Hepatocyte-like Cells Exhibiting Functional Activities. *Cloning Stem Cells* 9(1): 51–62.

18 Cortesini R (2005) Stem cells, tissue engineering and organogenesis in transplantation. *Transpl Immunol* 15(2): 81–89.

19 Rogers I and Casper RF (2003) Stem cells: you can't tell a cell by its cover. *Hum Reprod Update* 9(1): 25–33.

stem cells called MAPCs, taken from the bone marrow of mice could grow into an array of biological tissues, including brain, heart, lung and liver.[20] Unfortunately, these results proved to be very difficult to replicate and have recently come under intense scrutiny. In 2007, a panel of experts commissioned by the University of Minnesota concluded that the process by which the tissue from adult stem cells was identified was significantly flawed and that the conclusions reached by the authors on the basis of these data, were potentially incorrect. The panel found that the flaws identified in the paper were mistakes rather than falsifications.[21] In response to the investigation, the journal *Nature* convened their own expert panel to review the data from the landmark 2002 paper. The experts concluded that although the data contained in some figures were flawed, the paper's conclusions were still valid.[22] Verfaillie, also maintains that the problems identified with the data did not affect the study's conclusions about the potential plasticity of adult stem cells and in 2007, a correction to the original data was published in *Nature*.[23]

There is currently a vigorous discussion in the scientific community about the capability of adult stem cells to differentiate across tissue lineage boundaries. Reports describing adult stem cell plasticity initially caused much excitement, due to their potential ability to provide an easily accessible source of cells, which would not be marred by ethical considerations. Pluripotent stem cell populations have been cultured from skin (SKPs)[24], bone marrow (hBMSCs[25], MIAMI[26], MAPCs[27]) and umbilical cord blood (USSCs[28]). Given that these cells were selected after extensive manipulation in the laboratory, it is possible that they do not exist *in vivo*, but are a culture induced phenomenon. The existence of adult stem cell plasticity has been attributed to cell fusion, spontaneous reprogramming by culture and even cross contamination of cell cultures.[29] Further research is required to determine whether truly pluripotent stem cells persist beyond gastrulation.

Induction of pluripotency in adult stem cells is an active area of research and has recently yielded significant results. (See section on Dedifferentiation for details).

20 Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, *et al.* (2002) Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 418(6893): 41–49.

21 Holden C (2007) Data on Adult Stem Cells Questioned. *Science* 315(5816): 1207.

22 Check E (2007b) Stem-cell paper corrected. *Nature* 447(7146): 763.

23 Jiang Y, Jahagirdar BN, Reinhardt RE, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, *et al.* (2007) Corrigendum: Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 447(7146): 879–80.

24 Toma JG, McKenzie IA, Bagli D, Miller FD (2005) Isolations and Characterization of Multipotent Skin-Derived Precursors from Human Skin. *Stem Cells* 23(6): 727–737.

25 Yoon Y-S, Wecker A, Heyd L, Park J-S, Tkebuchava T, Kusano K, *et al.* (2005) Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction. J Clin Invest 115(2): 326-338.

26 D'Ippolito G, Diabira S, Howard GA, Menei P, Roos BA, and Schiller PC (2004) Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential. *J Cell Sci* 117(14): 2971–2981.

27 Jiang Y, *et al.* (2002) *op. cit.*

28 Kögler G, Sensken S, Airey JA, Trapp T, Müschen M, Feldhahn N, *et al.* (2004) A New Human Somatic Stem Cell from Placental Cord Blood with Intrinsic Pluripotent Differentiation Potential. *J Exp Med* 200(2): 123–135.

29 Wagers AJ and Weissman IL (2004) Plasticity of Adult Stem Cells. *Cell* 116(5): 639–648.

Umbilical Cord Blood Stem Cells

Stem cells have also been found in umbilical cord blood and can be preserved at the birth of a child. Cord blood stem cells are more flexible than most types of adult stem cells, as they have the potential to give rise to a variety of cell types other than blood cells, such as bone, neural and endothelial cells. When cultured *in vitro*, cord blood stem cells have been shown to differentiate into osteoblasts (bone cells), chondroblasts (cartilage cells), adipocytes (fat cells) and neural cells. In terms of their potential to differentiate into a wide variety of specialised cells, cord blood stem cells appear to be situated somewhere in between embryonic stem cells and other types of adult stem cells.[30] In 2005, cord blood derived "embryonic like" stem cells were isolated. These stem cells were successfully expanded *in vitro and* were able to differentiate into cells destined to be liver cells, as well as into pancreatic cells.[31]

Recently, researchers have identified and isolated endometrial stem cells in menstrual blood.[32] These cells express typical adult stem cell markers as well as the embryonic stem cell marker OCT-4. Despite the fact that endometrial stem cells possess many of the same characteristics as mesenchymal stem cells present in the umbilical cord and bone marrow, endometrial stem cells proliferate (multiply) at a substantially faster rate. Thus, these cells may lie somewhere in between adult and embryonic stem cell in terms of their potential for differentiation. The researchers successfully differentiated the endometrial stem cells into nine different cells types, including fat, bone, nerve, liver and heart cells. The authors contend that given the ease with which these cells can be collected and expanded *in vitro*, as well as their ability to differentiate into different cell types, they can be banked for future use.

Applications of Adult Stem Cells

Adult stem cells have also been intensively studied for their potential use in cell therapies for neurological disorders, such as Huntington's disease. Huntington's disease is a fatal disorder characterised by chorea (excessive spontaneous movements) and progressive dementia and it is caused by the death of particular brain cells. Stem cell based approaches to treating Huntington's disease are still in their infancy, however, human neural stem cells implanted into the brains of rats with experimental Huntington's disease have been found to reduce motor impairments.[33,34] The stem cells did not actually replace or repair the damaged cells but their presence was beneficial.

30 Kögler G, *et al*. (2004) *op. cit*.

31 McGuckin CP, Forraz N, Baradez M-O, Navran S, Zhao J, Urban R, *et al*. (2005) Production of stem cells with embryonic characteristics from human umbilical cord blood. *Cell Prolif* 38(4): 245–255.

32 Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, *et al*. (2007) Endometrial regenerative cells: A novel stem cell population. *J Transl Med* 5(1): 57.

33 Ryu JK, Kim J, Cho SJ, Hatori K, Nagai A, Choi HB, *et al*. (2004) Proactive transplantation of human neural stem cells prevents degeneration of striatal neurons in a rat model of Huntington disease. *Neurobiol Dis* 16(1): 68–77.

34 McBride JL, Behrstock SP, Chen E-Y, Jakel RJ, Siegel I, Svendsen CN and Kordower JH (2004) Human neural stem cell transplants improve motor function in a rat model of Huntington's disease. *J Comp Neurol* 475(2): 211–219.

Myocardial infarction is the leading cause of heart failure in developed countries and heart cells have a very limited regenerative capacity after injury. In 2004, a German clinical trial of patients having suffered heart infarction showed improvement among those patients who received an injection of their own bone marrow stem cells following the event.[35] Groups in France and America are also investigating the potential effect of a patient's own bone marrow stem cells on heart recovery after infarction. The results have been mixed: out of four French studies, three were negative. One of the main problems is that in bone marrow, only 0.01% of the cells are stem cells and during transplant about 50% of these cells are lost. Another French group is looking at the potential of adult muscle stem cells for the same treatment and have shown encouraging results in ten patients.[36]

Adult stem cells also appear to have potential for the treatment of autoimmune disease. Brazilian and US scientists have recently reported preliminary results that indicate adult stem cell therapy may be of use in Type 1 diabetes treatment. Type 1 diabetes is caused by the patient's immune system destroying its own insulin producing cells in the pancreas. In the study in question, newly diagnosed young diabetes patients were given transfusions of their own stem cells and all but one of fifteen were able to survive without insulin injections for several months.[37]

Multiple sclerosis is an autoimmune disease that affects the central nervous system, which consists of the brain, spinal cord and the optic nerves. Surrounding and protecting nerve fibres is a fatty tissue called myelin. In multiple sclerosis, the myelin, which helps nerve fibres conduct electrical impulses, is lost in multiple areas, leaving scar tissue called sclerosis and producing the various symptoms of multiple sclerosis. In 2003, scientists in Italy injected neural stem cells, taken from the adult brains of mice, into the bloodstream of mice with a multiple sclerosis like disease and found that some of the cells migrated to damaged areas in the brain and spinal cord.[38] A subsequent study by the same team suggests that the main benefit of the neural stem cells on the mice brains is a bystander effect on the immune cells already present and this protects nerve fibres from additional damage.[39]

35 Wollert KC, Meyer GP, Lotz J, Ringes Lichtenberg S, Lippolt P, Breidenbach C, *et al.* (2004) Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 364(9429): 141–148.

36 Menasché P, Hagège A, Vilquin J-T, Desnos M, Abergel E, Pouzet B, *et al.* (2003) Autologous skeletal myoblast transplantation for severe postinfarction ventricular dysfunction. *J Am Coll Cardiol* 41(7): 1078–1083.

37 Voltarelli JC, Couri CEB, Stracieri ABPL, Oliveira MC, Moraes DA, Pieroni F, *et al.* (2007) Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus. *JAMA* 297(14): 1568–1576.

38 Pluchino S, Quattrini A, Brambilla E, Gritti A, Salani G, Dina G, *et al.* (2003) Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature* 422(6933): 688–694.

39 Pluchino S, Zanotti L, Rossi B, Brambilla E, Ottoboni L, Salani G, *et al.* (2005) Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* 436(7048): 266–271.

Applications of Cord Blood Stem Cells

It has long been known that umbilical cord blood contains a rich source of haematopoietic, or blood forming, adult stem cells that can be used to reconstitute the blood and immune system.[40] In the last 15 to 20 years, umbilical cord stem cells have been used as an alternative source of bone marrow for transplantation in patients, predominantly children, suffering from haematological malignancies, genetic immunodeficiencies and metabolic disorders.[41] Despite the fact that umbilical cord blood contains about one tenth of the number of stem cells found in bone marrow, it has a number of advantages over bone marrow and peripheral blood stem cells for haematopoietic transplantation. These include: faster availability, extension of the donor pool, a reduced incidence of viral transmission and a lower risk of rejection. A number of countries have, therefore, established accredited public banks that store haematopoietic stem cells, derived from umbilical cord blood, for transplant purposes.

To date, no clinical trials using cord blood stem cells for cardiovascular disease have been conducted in humans. However, since 2004, a number of preclinical studies have been performed in mouse and rat models, in which transplantation of cord blood stem cells after myocardial infarction significantly improved cardiac function compared with control animals.[42,43] The beneficial effects have been attributed to the induction of angiogenesis (the growth of new blood vessels), likely due to the fact that cord blood stem cells can differentiate into endothelial cells, the building blocks of blood vessels.[44]

It has also been demonstrated that human umbilical cord blood derived stem cells can be engineered to synthesise insulin, which has implications for the future treatment of diabetes.[45] Treatment of mice with Type 1 diabetes with cord blood stem cells lowered their blood glucose levels and increased their lifespan compared to control diabetic animals.[46,47] Using similar protocols to those established in animal studies, scientists at the University of Florida are currently evaluating the effects of cord blood stem cell transfusion in children with Type 1 diabetes.[48] The study is due to conclude in mid 2009.

40 Knudtzon S (1974) In Vitro Growth of Granulocytic Colonies From Circulating Cells in Human Cord Blood. *Blood* 43(3): 357–361.

41 Brunstein CG, Setubal DC and Wagner JE (2007) Expanding the role of umbilical cord blood transplantation. *Br J Haematol* 137(1): 20–35.

42 Amado LC, Saliaris AP, Schuleri KH, St John M, Xie J-S, Cattaneo S, *et al.* (2005) Cardiac repair with intramyocardial injection of mesenchymal stem cells after myocardial infarction. *PNAS* 102(32): 11474–11479.

43 Hirata Y, Sata M, Motomura N, Takanashi M, Suematsu Y, Ono M and Takamoto S (2005) Human umbilical cord blood cells improve cardiac function after myocardial infarction. *Biochem Biophys Res Commun* 327(2): 609–614.

44 Ma N, Stamm C, Kaminski A, Li W, Kleine H-D, Müller-Hilke B, *et al.* (2005) Human cord blood cells induce angiogenesis following myocardial infarction in NOD/*scid*-mice. *Cardiovasc Res* 66(1): 45–54.

45 Denner L, Bodenburg Y, Zhao JG, Howe M, Cappo J, Tilton RG, *et al.* (2007) Directed engineering of umbilical cord blood stem cells to produce C-peptide and insulin. *Cell Prolif* 40(3): 367–380.

46 Ende N, Chen R and Reddi AS (2004) Effect of human umbilical cord blood cells on glycemia and insulinitis in type 1 diabetic mice. *Biochem Biophys Res Commun* 325(3): 665–669.

47 Ende N, Chen R and Mack R (2002) NOD/LtJ type 1 diabetes in mice and the effect of stem cells (Berashis) derived from human umbilical cord blood. *J Med* 33(1–4): 181–187.

48 University of Florida, Juvenile Diabetes Research Foundation and National Institutes of Health (2007) *Umbilical Cord Blood Infusion to Treat Type 1 Diabetes*. ClinicalTrials.gov Identifier: NCT00305344. Available online at: http://www.clinicaltrials.gov/ct/show/NCT00305344?order=1, accessed 7 October 2007.

Foetal Stem Cells

Foetal stem cells are obtained from foetuses spontaneously[49] or electively aborted during early pregnancy (five-to-nine weeks post fertilisation). Foetal stems cells can be isolated from foetal blood and bone marrow,[50,51] as well as from other foetal tissues, including liver and kidney.[52,53] Foetal stem cells are described as being multipotent, although research suggests that foetal stem cells can differentiate into more cell types and multiply more readily than their adult counterparts.[54,55]

Even more versatile foetal stem cells have also been isolated. As mentioned previously, pluripotent embryonic like stem cells can be derived from foetal reproductive tissue; this was first achieved using primordial germ cells from mouse foetal tissue.[56] John Gearhart *et al.* isolated human primordial germ cells—the cells that will go on to become eggs and sperm—from five-to-nine week old foetal tissue obtained after pregnancy termination.[57] When grown in culture, these foetal stem cells maintained the same capacity to differentiate as embryonic stem cells.

Recently, scientists have discovered stem cells in amniotic fluid, which surrounds the unborn foetus. These stem cells are thought to be shed by the developing foetus and can be relatively easily retrieved during pregnancy (*e.g.* during amniocentesis). These cells may also have the potential to form multiple cell types.[58]

49 Spontaneous abortion refers to miscarriage.

50 Huss R (2000) Isolation of Primary and Immortalized CD34- Hematopoietic and Mesenchymal Stem Cells from Various Sources. *Stem Cells* 18(1): 1–9.

51 Waller EK, Olweus J, Lund-Johansen F, Huang S, Nguyen M, Guo GR and Terstappen L (1995) The "common stem cell" hypothesis reevaluated: human fetal bone marrow contains separate populations of hematopoietic and stromal progenitors. *Blood* 85(9): 2422–2435.

52 Campagnoli C, Roberts IAG, Kumar S, Bennett PR, Bellantuono I and Fisk NM (2001) Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver and bone marrow. *Blood* 98(8): 2396–2402.

53 Almeida-Porada G, El Shabrawy D, Porada C and Zanzani ED (2002) Differentiative potential of human metanephric mesenchymal cells. *Exp Hematol* 30(12): 1454–1462.

54 Guillot PV, Gotherstrom C, Chan J, Kurata H and Fisk NM (2007) Human first-trimester fetal MSC express pluripotency markers and grow faster and have longer telomeres than adult MSC. *Stem Cells* 25(3): 646–654.

55 O'Donoghue K and Fisk NM (2004) Fetal stem cells. *Best Pract Res Clin Obstet and Gynaecol* 18(6): 853–875.

56 Resnick JL, Bixler LS, Cheng L and Donovan PJ (1992) Long-term proliferation of mouse primordial germ cells in culture. *Nature* 359(6395): 550–551.

57 Gearhart J (1998) *op. cit*.

58 De Coppi P, Bartsch G Jr, Siddiqui MM, Xu T, Santos CC, Perin L, *et al.* (2007) Isolation of amniotic stem cell lines with potential for therapy. *Nat Biotechnol* 25(1): 100–106.

Applications of Foetal Stem Cells

In clinical trials, patients suffering from Parkinson's disease have received transplants of foetal stem cells from the brain tissue of aborted foetuses. Although the transplanted cells were shown to produce long lasting (up to ten years) symptomatic improvement in some patients, there were significant associated side effects, such as dyskinesia (difficulty in performing voluntary movements).[59] Two controlled surgical trials[60,61] showed only modest improvements in patients, with significantly fewer transplanted neurons surviving than in earlier trials. However, a recent study in a monkey model of the brain disorder has renewed hope to some extent. Researchers injected human foetal brain stem cells into the brains of monkeys with a severe form of chemically induced Parkinson's disease. Before the treatment, the monkeys could not walk unaided and struggled to use their hands but two months afterwards, they could walk and feed themselves normally.[62] Unfortunately, another two months later, the monkeys started once again to show symptoms of the disease. The researchers think this may be due to the monkeys beginning to reject the foreign cells and they suggest that further research suppressing the monkeys' immune system should be undertaken.

Foetal stem cell transplantation has also been used in patients suffering from Huntington's disease. The extent of clinical benefit is, however, unclear. One trial documented cognitive and motor improvements,[63] whereas in another trial no effect was seen.[64] The transplantation of human foetal stem cells to treat neurodegenerative disorders is limited by the availability of foetal tissue.

Children born with rare tracheal defects cannot breathe and must immediately receive intensive care. They often suffer from neurological and other complications of heart–lung bypass and the best treatments developed so far involve using pieces of the infant's rib, pelvic bone or Teflon, to reconstruct the incomplete, malformed or missing trachea. Sheep amniotic stem cells have been used to engineer new tracheas in unborn lambs with tracheal defects.[65] In 2005, researchers at the Children's Hospital Boston isolated mesenchymal stem cells from the amniotic fluid surrounding unborn lambs with tracheal defects. They "seeded" the cells on biodegradable tube shaped scaffolds and put them in an environment that caused them to differentiate into cartilage cells. When the engineered grafts were "grown", they were used to reconstruct the foetal tracheas *in utero*, that is, while the lambs were still in their mother's uterus.

59 Lindvall O, Kokaia Z and Martinez-Serrano A (2004) Stem cell therapy for human neurodegenerative disorders—how to make it work. *Nat Med* 10(7 Supplement): S42–50.

60 Freed CR, Greene PE, Breeze RE, Tsai W-Y, DuMouchel W, Kao R, *et al*. (2001) Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease. *N Engl J Med* 344(10): 710–719.

61 Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, *et al*. (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol* 54(3): 403–414.

62 Redmond DE Jr, Bjugstad KB, Teng YD, Ourednik V, Ourednik J, Wakeman DR, *et al*. (2007) Behavioral improvement in a primate Parkinson's model is associated with multiple homeostatic effects of human neural stem cells. *PNAS* 104(29): 12175–12180.

63 Bachoud-Lévi A-C, Rémy P, Nguyen J-P, Brugières P, Lefaucheur J-P, Bourdet C, *et al*. (2000) Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. *Lancet* 356(9246): 1975–1979.

64 Hauser RA, Furtado S, Cimino CR, Delgado H, Eichler S, Schwartz S, *et al*. (2002) Bilateral human fetal striatal transplantation in Huntington's disease. *Neurology* 58(5): 687–695.

65 Shay M-E (2005) Cells from amniotic fluid used to tissue-engineer a new trachea. *Medical News Today*, 11 October 2005. Available online at: http://www.medicalnewstoday.com/medicalnews.php?newsid=31834, accessed 3 December 2007.

Benefits and Limitations of Different Types of Stem Cells

Since the use of stem cells derived from embryonic material is highly controversial, there has been a lot of discussion about which stem cells are most suitable for stem cell research and which have the most potential for delivering stem cell therapies.

One of the main focuses of the discussion has been on the ability of various stem cells to differentiate into a range of cell types, which may be useful in cell therapy. Indeed, stem cells differ considerably in the amount and type of different cells they can become. Embryonic stem cells are either totipotent or pluripotent and can give rise to all of the cell types of the body, whereas adult stem cells are predominantly multipotent, meaning they are generally limited to specialising into the different cell types of their tissue of origin. The distinction between adult and embryonic stem cells is popular for the purposes of the ethical discussion surrounding research involving the destruction of embryos. However, the emerging consensus among stem cell researchers is that a continuum of stem cell types exists, with foetal stem cells, for example, lying somewhere in between embryonic and adult stem cells in terms of their ability to form a variety of specialised cell types.

Another major focus of the discussion of the various stem cells' potential for therapy has been on their susceptibility to produce an immune response in patients. Using stem cells for therapeutic purposes has much in common with the well established practise of organ transplantation, except that in stem cell therapy, a population of cells, rather than an organ, is introduced into a patient. One of the main challenges for stem cell therapy development is to avoid immune reactions, which, as in the case of organ rejection following transplantation, are triggered by the introduction of foreign cells into a patient's body.

Structures called antigens, which are present on the surface of cells, are the signals by which the immune system recognises external cells and proceeds to reject them. Embryonic stem cells and multipotent stem cells from the foetus, amniotic fluid and umbilical cord blood have an advantage over stem cells from the adult body because they express less antigen molecules on their cell surface.[66] Stem cells presenting lower levels of antigens may not fully escape an immune reaction but they may trigger a milder or a delayed response. Adult stem cells, on the other hand, can potentially be taken from a patient's own body and would not, therefore, be rejected by the immune system. This approach is referred to as patient specific therapy.

Another challenge for all stem cell types is to produce high quality stocks of cells for any future cell replacement therapies. Large numbers of cells will be needed for such therapies and the availability of stem cells, as well as their ability to grow *in vitro* will, therefore, be crucial to their success in the clinic. Embryonic stem cells grow relatively easily in culture, once they are established as a cell line. Recent advances have been made in replacing culture medium containing animal products with culture that includes protein components solely derived from recombinant sources or human material.[67]

66 Götherström C, Ringdén O, Tammik C, Zetterberg E, Westgren M and Le Blanc K (2004) Immunologic properties of human fetal mesenchymal stem cells. *Am J Obstet Gynecol* 190(1): 239–245.

67 Tenneille LE, Levenstein ME, Jones JM, Berggren WT, Mitchell ER, Frane JL, *et al.* (2006) Derivation of human embryonic stem cells in defined conditions. *Nat Biotechnol* 24(2): 185–187.

This is an important step towards developing the potential of embryonic stem cells, as "clean" cells, which will be needed for use in human therapy. Adult stem cells are rare in mature tissues, often difficult to isolate and methods for expanding their numbers in the laboratory have not yet been perfected. Their growth is nevertheless more regular/predictable *in vitro* than that of embryonic stem cells.

The therapeutic use of stem cells is also limited by their ability to divide vigorously. Embryonic stem cells, in particular, have the ability to divide indefinitely, like cancer cells and have been shown in animals to have the potential to form tumours called teratomas when transplanted. There is less risk of tumours resulting from cell replacement therapy using adult stem cells, due to their growth properties. Generally speaking, stem cells must be very carefully differentiated into specialised cells before they are used for treatment because any remaining stem cells could potentially grow out of control and form tumours. It has also recently been shown that adult stem cells may become cancerous following long term growth *in vitro*, which further suggests that caution is warranted in terms of their use.[68]

At present, it is very difficult to predict which type of stem cell might be most successful in treating various diseases and conditions. A good example of the current uncertainty is research into stem cell therapy for treating Parkinson's disease. Although most of the research so far has been done using foetal stem cells, differentiated neurons with the properties of those destroyed by the progress of Parkinson's disease have also been generated *in vitro* from embryonic stem cells, as well as from adult stem cells found in bone marrow.[69,70] The case is similar for other research areas, such as the treatment of heart infarction. Most of the current research into heart stem cell therapy is focusing on adult stem cells but some success has been obtained with embryonic and foetal stem cells.[71,72] For the treatment of multiple sclerosis, adult and embryonic stem cells have both been shown to be capable of myelinating damaged mouse brain and spinal cord nerves after transplantation.[73,74]

Many scientific bodies converge on the view that research using all types of stem cells, including human embryonic stem cells, represents the optimal strategy for the advance of stem cell research and the delivery of therapies.[75,76,77]

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68 Rubio D, Garcia-Castro J, Martín MC, de la Fuente R, Cigudosa JC, Lloyd AC and Bernad A (2005) Spontaneous Human Adult Stem Cell Transformation. *Cancer Res* 65(8): 3035–3039.

69 Dezawa M, Kanno H, Hoshino M, Cho H, Matsumoto N, Itokazu Y, *et al*. (2004) Specific induction of neuronal cells from bone marrow stromal cells and application for autologous transplantation. *J Clin Invest* 113(12): 1701–1710.

70 Takagi Y, Takahashi J, Saiki H, Morizane A, Hayashi T, Kishi Y, *et al*. (2005) Dopaminergic neurons generated from monkey embryonic stem cells function in a Parkinson primate model. *J Clin Invest* 115 (1): 102–109.

71 Davani S, Deschaseaux F, Chalmers D, Tiberghien P and Kantelip J-P (2005) Can stem cells mend a broken heart? *Cardiovasc Res* 65(2): 305–316.

72 Geron Corporation is developing embryonic stem cell derived heart cells for treating myocardial infarction. More information is available online at: http://www.geron.com/showpage.asp?code=prodsthr

73 Windrem MS, Nunes MC, Rashbaum WK, Schwartz TH, Goodman RA, McKhann II G, *et al*. (2004) Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. *Nat Med* 10(1): 93–97.

74 Nistor GI, Totoiu MO, Haque N, Carpenter MK and Keirstead HS (2005) Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. *Glia* 49(3): 385–396.

75 US National Institutes of Health (2001) *NIH Statement on the President's Stem Cell Address*. NIH News Advisory, published 9 August 2001. Available online at: http://www.nih.gov/news/pr/aug2001/od-09.htm; accessed 13 November 2007: "We believe this combined [embryonic and adult stem cell] research has high potential both for opening new doors in basic scientific understanding and for discovery of new treatments for some of our most devastating diseases".

76 The Royal Society (2001) *Stem cell research—second update*. London. Available online at: http://www.royalsoc.ac.uk/displaypagedoc.asp?id=11473, accessed 13 November 2007: "The Royal Society believes that adult stem cell research and embryonic stem cell research are not alternatives and both must be pursued".

77 European Molecular Biology Organisation (2006) *Stem Cell Research: Status, Prospects and Prerequisites*. Heidelberg, Germany: "Recommendation #2: Research on both adult and embryonic stem cells, being highly complementary, should be fully supported", p.9.

Table 1. Characteristics of Embryonic and Adult Stem Cells

Embryonic Stem Cells	Adult Stem Cells
They are relatively plentiful and are easier to grow in the laboratory than adult stem cells.	They are present in very small numbers and are difficult to access. They can also be difficult to grow in the laboratory.
They can develop into any type of cell found in the body.	Currently, they are known to develop into a restricted number of different cell types, usually related to the type of tissue they are found in.
They would not be genetically matched to the individual being treated and could possibly be rejected by his or her immune system.	They can be genetically matched to the individual being treated and would not be rejected by his or her immune system.
If not fully differentiated into a cell type with a specialised function, embryonic stem cells can form tumours.	There is less evidence to suggest that cells and tissues derived from adult stem cells will develop tumours.

Sources of Embryonic Stem Cells

In Vitro Fertilisation

The main source of human embryonic stem cells for research is embryos produced, but not used, during IVF[78] for infertility treatment (known as supernumerary IVF embryos). First described in 1978, IVF is a technique that enables individuals with a wide range of fertility disorders to have children. In Ireland, there are currently nine clinics offering some form of assisted human reproduction (AHR), including IVF.[79] In brief, the IVF process involves the removal of eggs from a woman's ovary just before ovulation and the eggs are then combined with sperm in the laboratory. If fertilisation occurs, an embryo is formed and placed in a woman's uterus where it may implant, thus, leading to pregnancy.

During a natural menstrual cycle, one-to-two eggs develop and are available for fertilisation. The success rate of IVF treatment can be improved by hormonally stimulating a woman's ovaries to produce more eggs (average: 8, range: 3 to 40) to be collected and fertilised. It is standard practise in fertility clinics to use superovulation (ovarian stimulation) as part of the IVF procedure. The hormonal ovarian stimulation needed to harvest eggs can lead to ovarian hyper stimulation syndrome. The prevalence of the severe form of ovarian hyper stimulation syndrome is small, ranging from 0.5–5%, however, it can be fatal in its severest form.[80] The hormonal treatment may also lead to increased risk of hormone dependent cancers, such as breast, ovarian and uterine cancers.[81] All of the eggs retrieved are usually combined with sperm and approximately 70% will be fertilised.

78 *In vitro* fertilisation is a laboratory procedure in which sperm are placed with an unfertilised egg in a Petri dish to achieve fertilisation. The embryo is then transferred into the uterus to begin a pregnancy or cryopreserved (frozen) for future use.

79 For a description of assisted human reproductive services in Ireland, see the Commission on Assisted Human Reproduction (2005) *Report of the Commission on Assisted Human Reproduction*. Dublin.

80 Delvigne A and Rozenberg S (2002) Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Hum Reprod Update* 8(6): 559–577.

81 Pearson H (2006) Health effects of egg donation may take decades to emerge. *Nature* 442(7103): 607–608.

Of the embryos generated, not all will be healthy enough to lead to a pregnancy. Indeed, the embryos are graded according to their morphology and a high percentage of them undergo spontaneous "cleavage arrest", in which their cells simply stop dividing. In most cases, this is associated with genetic abnormalities in the cells of the developing embryo.[82,83] The first weeks of development are the most hazardous period of life. Even in natural conception, it has been estimated that roughly one third to half of all fertilised zygotes never make it beyond this point. Some suggest that the rate of natural embryo loss, including loss before and after implantation in the womb, is as high as 80%.[84]

In IVF treatment, the healthiest embryos (usually one-to-three) are transferred into the woman's uterus, with the hope being that at least one will successfully implant and lead to pregnancy. It is not recommended that more than three embryos be transferred, as multiple pregnancies are at increased risk of miscarriage, premature delivery and foetal or neonatal death. The most effective strategy for reducing the number of multiple births is to transfer a single embryo, however, this has usually been associated with a lower chance of a successful birth than the transfer of two or more embryos.[85] Recent evidence suggests, that the quality of the embryo and the time the embryo spends in culture prior to its placement in the womb are critical factors in increasing pregnancy rates with single embryo transfer.[86,87] In many cases, more embryos than can safely be used during one treatment cycle of IVF are generated, including unhealthy embryos that would not be considered for transfer to the womb. With the introduction of cryopreservation (freezing), excess embryos can now be stored so that the woman does not have to go through the ovarian stimulation and egg collection process prior to each cycle of IVF.

Ethical objections to the production and cryopreservation of embryos have been raised. Several emerging technologies may address the problem of producing more embryos than will be used to achieve pregnancies by AHR. First of all, there has been some improvement with natural cycle IVF treatment where one or two eggs are collected without the aid of hormonal stimulation. However, the efficiency of natural cycle IVF is still much lower than conventional IVF, which involves harvesting several eggs and producing multiple embryos that can be transferred to the womb. Given the costs and risks incurred by women undergoing infertility treatment, natural cycle IVF treatment is not yet regarded as the preferred option. Secondly, it is possible to freeze eggs fertilised by IVF at the pronuclear stage, that is, before the process of fertilisation is complete and the embryo is fully formed. This approach has been taken in Germany to avoid the ethical concerns associated with producing and storing human embryos. Finally, progress has been made in relation to egg freezing

82 Zhang X, Stojkovic P, Przyborski S, Cooke M, Armstrong L, Lako M and Stojkovic M (2006) Derivation of Human Embryonic Stem Cells from Developing and Arrested Embryos. *Stem Cells* 24(12): 2669–2676.

83 The reasons for the abnormalities and arrest of IVF embryos at various stages in early embryonic development are diverse and can include inadequate egg maturation; chromosomal irregularities during early cleavage; cellular asymmetry, including DNA, nuclear and cytoplasmic fragmentation; and suboptimal *in vitro* culture conditions.

84 The President's Council on Bioethics (2004a) *Monitoring Stem Cell Research*. Washington, DC, p.88.

85 van Montfoort APA, Fiddelers AAA, Janssen JM, Derhaag JG, Dirksen CD, Dunselmann GAJ, *et al.* (2006) In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. *Hum Reprod* 21(2): 338–343.

86 Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandel A and Bergh C. (2004) Elective Single-Embryo Transfer versus Double-Embryo Transfer in In Vitro Fertilization. *N Engl J Med* 351(23): 2392–2402.

87 Veleva Z, Vilska S, Hydén-Granskog C, Tiitinen A, Tapanainen JS, and Martikainen H (2006) Elective single embryo transfer in women aged 36–39 years. *Hum Reprod* 21(8): 2098–2102.

using a process called vitrification and this may eventually alter IVF practices. If, in the future, only a small percentage of the eggs are destroyed by the freezing–defrosting procedure and the embryos produced from frozen eggs are shown to be as healthy as those produced from freshly harvested eggs, fertility clinics may have the option of fertilising a few eggs at a time, thus, producing a limited number of embryos, without having to submit women to more cycles of egg harvesting than necessary. Although pregnancy rates using thawed eggs for IVF appear to be lower than those achieved with fresh eggs,[88] the live birth rates using thawed eggs compare favourably with those reported when frozen rather than fresh embryos are transferred to the womb.[89]

Nevertheless, the technical limitations of current reproductive technologies signify that, in the foreseeable future, embryos that will not be used to achieve a pregnancy will be produced during infertility treatment. If the embryos that are not used are donated for research, scientists remove stem cells from the embryos at the blastocyst stage and try to establish stem cell lines from these. This procedure results in the destruction of the embryo.

Somatic Cell Nuclear Transfer (Cloning)

Alternatively, embryonic stem cells can be obtained from embryos produced by somatic cell nuclear transfer (SCNT), a technique otherwise known as cloning. The term "clone" is generally used to define an organism that is a genetic copy of another existing organism. Dolly the sheep, cloned in 1996, remains the most famous clone to date.

Many species produce their offspring asexually, that is, without combining male and female genetic material. Such offspring are clones of their parent. Asexual reproduction is the primary form of reproduction for single celled organisms such as bacteria and is also seen in many plants. Cloning can also occur naturally in organisms that reproduce sexually. For example, clones are produced when a fertilised egg splits very early in development, yielding identical twins who possess the same genetic material.

Cloning *via* SCNT is a technique used for cloning an organism of a species that does not normally reproduce asexually. This technique was first used 40 years ago in research on tadpoles and frogs. Scientists were interested in the technique as a way of studying gene function in relation to development. In particular, they wondered whether genes necessary for development could be switched back on in differentiated adult cells in which they had long ceased to function. This turned out to be the case and SCNT effectively reset the gene expression of a differentiated somatic cell to a state consistent with embryonic development.

In SCNT, the nucleus of a somatic cell[90] is taken from an organism and transplanted into an egg that has had its own nucleus removed (an enucleated egg). The nucleus of the cell carries most of an individual's genetic material and, therefore, the egg is given the DNA of the individual to be cloned. The modified egg is then activated, by means of an electrical current or chemicals, to stimulate

88 Oktay K, Cil AP and Bang H (2006) Efficiency of oocyte cryopreservation: a meta-analysis. *Fertil Steril* 86(1): 70–80.

89 Jain JK and Paulson RJ (2006) Oocyte cryopreservation. *Fertil Steril* 86(4 Supplement 1): 1037–1046.

90 A somatic cell is any cell of the body except for sperm and egg cells, which are referred to as germ cells.

embryonic development. When the blastocyst stage is reached (after about five days of development), the cloned embryo can be transferred into a womb, where it may implant and lead to pregnancy. This is called reproductive cloning and can lead to the birth of a clone of the somatic cell donor. Alternatively, embryonic stem cells can be extracted from the five-day-old cloned embryo.

The cloned embryo is not an exact genetic copy of the DNA donor, since a small amount of cellular DNA resides outside of the nucleus in structures called mitochondria. Mitochondrial DNA (mtDNA) is passed on to children from their mothers. The clone and the donor would, therefore, be genetically identical if the egg came from the donor or from the donor's maternal line.

Scientists have successfully cloned a number of animals over the last decades, including cats, dogs, cows, horses, deer, pigs, rabbits, sheep, mice and rats. Nonetheless, reproductive cloning by SCNT is far from a perfected technique. The process remains highly inefficient, with less than a 1% chance of obtaining a live birth in the species in which it has been achieved. Furthermore, unpredicted genetic and epigenetic problems have arisen in all of the mammals cloned so far. These have led to a high rate of foetal abnormalities and prenatal death and to health problems for those animals born alive.

The interest in reproductive animal cloning is still largely driven by a desire to understand the fundamental processes of developmental biology. Applications of the technique centre mainly on producing herds of genetically identical animals (especially valuable genetically modified (GM) animals), such as the GM goats producing a human anti clotting protein in their milk that have recently been approved for use by the European Medicines Agency.[91] There is also great interest in producing cloned GM laboratory animals, which are valuable as models for research into human disease. The production of cloned cows, to be used for testing breeding bulls, has also been suggested as a potential application.[92]

Therapeutic *versus* Reproductive Cloning

Embryonic stem cells can be extracted from embryos produced by SCNT. Cloning carried out for this specific purpose is commonly referred to as therapeutic cloning, because the cloned embryo is made solely to obtain embryonic stem cells for research or therapy. Extracting stem cells from a blastocyst, whether produced by IVF or SCNT, leads to the destruction of the embryo. Referring to this application of SCNT as therapeutic cloning is not universally condoned, because embryonic stem cells have yet to prove their efficacy in therapy. In this Opinion, when referring to the use of SCNT to obtain cloned embryos from which stem cells can be isolated for research purposes, the terms "cloning for research purposes" or "research cloning", will be used.

91 European Medicines Agency (2006) *European Medicines Agency adopts first positive opinion for a medicinal product derived from transgenic biotechnology*. Press release, published 2 June 2006. Available online at: http://www.emea.europa.eu/pdfs/general/direct/pr/20316306en.pdf, accessed 22 June 2007.

92 Meyer G (2005) *Why clone farm animals? Goals, motives, assumptions, values and concerns among European scientists working with cloning of farm animals*. Denmark.

There is an important potential advantage to obtaining stem cells from cloned embryos rather than from embryos produced by IVF for infertility treatment. If embryonic stem cell therapies are developed, the somatic cell used for SCNT could be supplied by the patient. The embryonic stem cells isolated from the resulting cloned embryo would then be genetically similar to the patient's cells and would not, therefore, be likely to be rejected by his/her immune system. In this way, SCNT could allow patient specific embryonic stem cells to be generated (see Figure 3).

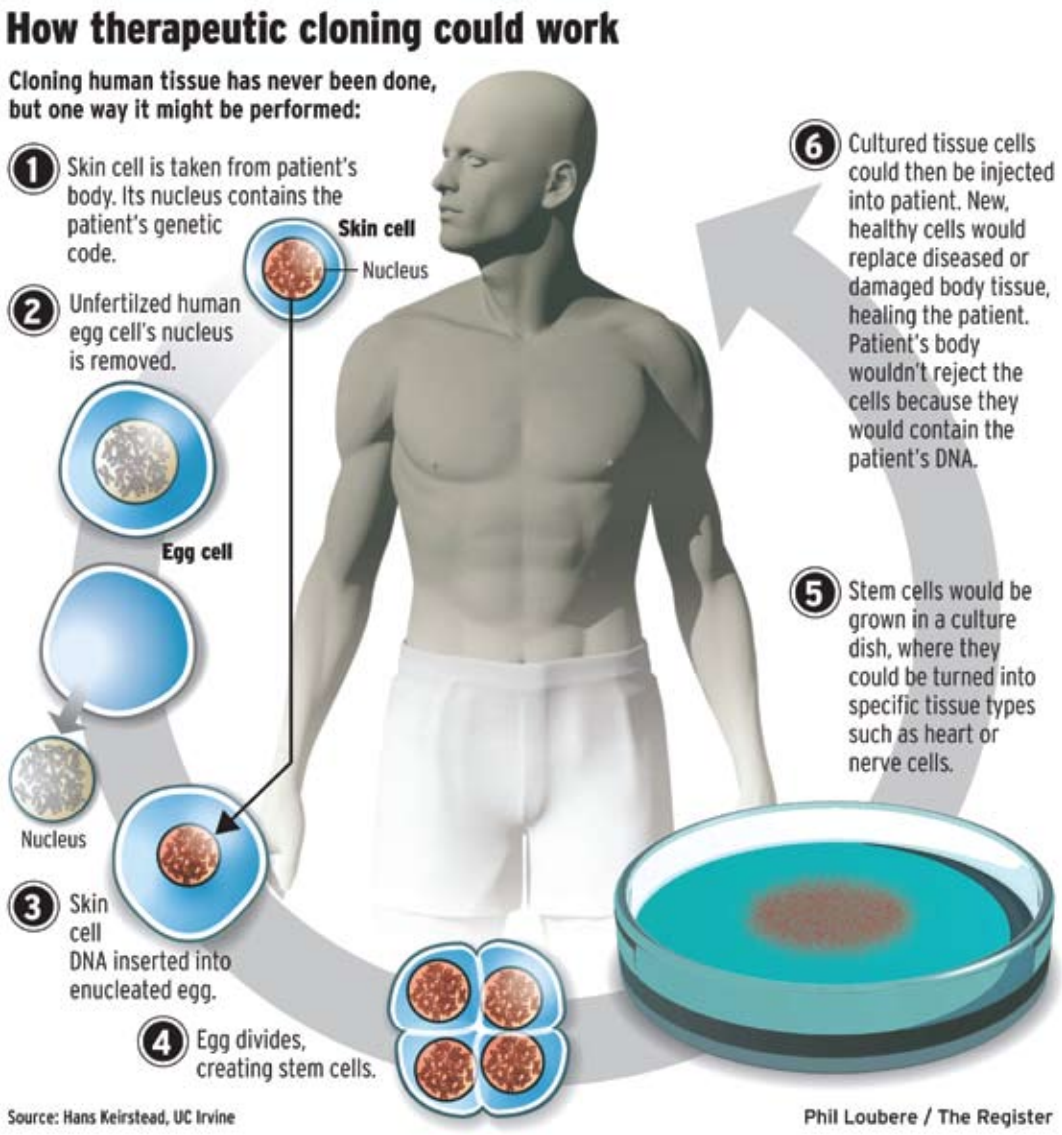

Figure 3. Research cloning for the purpose of deriving patient specific embryonic stem cells

Research Developments

Due to the promise of patient specific stem cells and the success of SCNT in mice,[93,94] there is considerable research interest in deriving human embryonic stem cells from cloned embryos. In 2004, South Korean researcher Hwang Woo Suk claimed to have cloned human embryos and derived patient specific embryonic stem cell lines from these embryos.[95,96] However, following a highly publicised investigation into his research, all of his human cloning work was found to be fraudulent and only "Snuppy", the Afghan hound Hwang had reported cloning, was found to be a genuine SCNT clone.[97,98,99]

In May 2005, a Newcastle University research team reported that they had produced human SCNT embryos using human embryonic stem cells as the source of nuclear DNA for the cloning. However, the researchers failed to establish embryonic stem cell lines from these cloned embryos.[100] In January 2008, a group of American scientists created five SCNT embryos using skin cells from two men and eggs donated by three women undergoing infertility treatment.[101] The researchers did not manage to extract any stem cells from the cloned embryos. Cloning in non human primates has also shown a low blastocyst development rate compared with other species and no pregnancies have been established from embryos cloned using differentiated somatic cell nuclei.[102] However, researchers from the Oregon National Primate Research Center have recently announced that they managed to establish embryonic stem cell lines from cloned monkey embryos. A total of 278 cloning attempts yielded 21 blastocysts, from which the team were able to derive two embryonic stem cell lines.[103,104,105] The authors acknowledge that even if the modified SCNT method worked in humans, a significant increase in SCNT embryo generation and embryonic stem cell derivation would have to be achieved in order to deliver any clinical applications. Nonetheless, human SCNT embryonic stem

93 Munsie MJ, Michalska AE, O'Brien CM, Trounson AO, Pera MF and Mountford PS (2000) Isolation of pluripotent embryonic stem cells from reprogrammed adult mouse somatic cell nuclei. *Curr Biol* 10(16): 989–992.

94 Kawase E, Yamazaki Y, Yagi T, Yanagimachi R and Pedersen RA (2000) Mouse embryonic stem (ES) cell lines established from neuronal cell-derived cloned blastocysts. *Genesis* 28(3–4): 156–163.

95 Hwang WS, Ryu YJ, Park JH, Park ES, Lee EG, Koo JM, *et al.* (2004) Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst. *Science* 303(5664): 1669–1674.

96 Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK, Kim S, *et al.* (2005) Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts. *Science* 308(5729): 1777–1783.

97 Seoul National University Investigation Committee (2006) *Summary of the Final Report on Hwang's Research Allegation.* Available online at: http://www.useoul.edu/sk _ board/boards/sk _ news _ read.jsp?board=11769&id=26092&p=1&p _ tid=26084, accessed 14 March 2007.

98 Kennedy D (2006) Editorial Retraction. *Science* 311(5759): 335.

99 Science (2006) *Science* Editorial Statement Concerning Stem Cell Manuscripts by Woo Suk Hwang *et al.* 12th Jan 2006. *Science*, published online at: http://www.sciencemag.org/sciext/hwang2005/science _ statement.pdf, accessed 14 March 2007.

100 Stojkovic M, Stojkovic P, Leary C, Hall VJ, Armstrong L, Herbert M, *et al.* (2005) Derivation of a human blastocyst after heterologous nuclear transfer to donated oocytes. *Reprod Biomed Online* 11(2): 226–231.

101 French AJ, Adams CA, Anderson LS, Kitchen JR, Hughes MR and Wood SH. (2008) Development of Human Cloned Blastocysts Following Somatic Cell Nuclear Transfer with Adult Fibroblasts. *Stem Cells* 26(2): 485–493.

102 Simerly C, Navara C, Hyun SH, Lee BC, Kang SK, Capuano S, *et al.* (2004) Embryogenesis and blastocyst development after somatic cell nuclear transfer in nonhuman primates: overcoming defects caused by meiotic spindle extraction. *Dev Biol* 276(2): 237–252.

103 This research was announced on 18 June 2007 at the annual meeting of the International Society for Stem Cell Research.

104 Baker M (2007) Monkey stem cells cloned. *Nature* 447(7147): 891.

105 Byrne JA, Pederson DA, Clepper LL, Nelson M, Sanger WG, Gokhale S, *et al.* (2007) Producing primate embryonic stem cells by somatic cell nuclear transfer. *Nature* 450(7169): 497–502.

cells would be valuable for research aimed at understanding molecular mechanisms underlying disease symptoms.[106] Obtaining human embryonic stem cells from cloned embryos is proving difficult but at least three groups in the US, three in Europe and one in China are currently pursuing this goal.

Egg Free Cloning

Due to its inefficiency, cloning requires a large supply of human eggs, which are usually donated through IVF programmes. As the production and extraction of eggs involves considerable risks for women donors, it seems unlikely that voluntary egg donation will provide a sufficient supply for future research needs.[107]

A potential solution to the problem of egg supply for cloning has recently been published.[108] The authors describe how mice have successfully been cloned by inserting the nuclear DNA of a somatic cell into a zygote rather than an unfertilised egg. The team was able to derive embryonic stem cell lines from the cloned embryos. If the technique can be replicated in humans, it could reduce the dependence of cloning on a supply of fresh eggs. Researchers could use frozen early stage IVF embryos, including those that are not suitable for pregnancy due to chromosomal abnormalities, instead of eggs. Scientists have also recently reported that they were able to produce human SCNT embryos using *in vitro* matured oocytes.[109] This means that it may be possible to use ovarian tissue, which can be obtained posthumously or after ovary removal for clinical reasons, as a source of eggs for cloning. Alternatively, it may soon be possible to generate eggs from embryonic stem cells. Stem cell technology may allow fully functional gametes to be produced from embryonic stem cells.[110] In the last few years, several reports have shown that mouse embryonic stem cells can differentiate into sperm[111] and ova.[112] Preliminary data indicate that human embryonic stem cells most likely display a similar capacity.[113] If in the future, such gametes prove to be fully functional, embryonic stem cells could provide a renewable source of eggs for cloning.[114]

106 Byrne JA, Mitalipov SM, and Wolf DP (2006) Current progress with primate embryonic stem cells. *Curr Stem Cell Res Ther* 1(2): 127–138.

107 The Academy of Medical Sciences (2007) *Inter-species embryos. A report by the Academy of Medical Sciences.* London.

108 Egli D, Rosains J, Birkhoff G and Eggan K (2007) Developmental reprogramming after chromosome transfer into mitotic mouse zygotes. *Nature* 447(7145): 679–685.

109 Heindryckx B, De Sutter P, Gerris J, Dhont M and Van der Elst J (2007) Embryo development after successful somatic cell nuclear transfer to in vitro matured human germinal vesicle oocytes. *Hum Reprod* 22(7): 1982–1990.

110 Nagy ZP and Chang C-C (2007) Artificial gametes. *Theriogenology* 67(1): 99–104.

111 Toyooka Y, Tsuenekawa N, Akasu R, and Noce T (2003) Embryonic stem cells can form germ cells *in vitro*. *PNAS* 100(20): 11457–11462.

112 Hübner K, Fuhrmann G, Christenson LK, Kehler J, Reinbold R, De La Fuente R, *et al.* (2003) Derivation of Oocytes from Mouse Embryonic Stem Cells. *Science* 300(5623): 1251–1256.

113 Clark AT, Bodnar MS, Fox M, Rodriquez RT, Abeyta MJ, Firpo MT and Reijo Pera RA (2004) Spontaneous differentiation of germ cells from human embryonic stem cells *in vitro*. *Hum Mol Genet* 13(7): 727–739.

114 Evans M (2005) Ethical sourcing of human embryonic stem cells—rational solutions? *Nat Rev Mol Cell Biol* 6(8): 663–667.

Human-Animal Hybrids

Another solution that has been proposed to overcome the short supply of human eggs for cloning research is to use animal eggs. Transferring human DNA from the nucleus of a somatic cell into an enucleated animal egg, most likely from a cow or rabbit, would produce what has been referred to as a cytoplasmic human-animal hybrid embryo. The embryo would be allowed to develop *in vitro* for approximately five days, after which time embryonic stem cells would be extracted from the inner cell mass of this embryo, now a blastocyst.

Cytoplasmic human-animal hybrids are distinct from other types of interspecies embryos. A "true" hybrid results from the fusion of human and animal gametes and involves a combination of nuclear DNA from both sources. A chimeric embryo, or chimera, refers to an entity created by mixing embryos or cells and embryos from the same or from two different species. The proposal under consideration in this report is whether the creation of cytoplasmic human-animal hybrid embryos is an appropriate ethical response to the shortage of human eggs for SCNT. Therefore, true hybrids and chimeras will not be further discussed.

In 2003, a number of researchers reported successfully having created cytoplasmic human-animal hybrid embryos. A team of scientists at Cambridge University transferred the nuclei of adult human cells into immature frog eggs.[115] A group of scientists in China reported using enucleated rabbit eggs as hosts for human fibroblasts and cells with embryonic like properties were harvested from the human-rabbit hybrid embryos.[116] These cells were capable of differentiating into a wide range of cell types *in vitro*. Chang *et al.* have demonstrated that a human nucleus transferred into a cow egg can develop into an early embryo.[117] Scientists are hopeful that the creation of cytoplasmic human-animal hybrid embryos will provide a source of embryonic stem cells for research and perhaps even therapeutic applications, in the future. Advanced Cell Technologies (a biotechnology company focused on developing and commercialising human stem cell technology) has patented a technique for generating embryos by fusing human nuclei with bovine eggs.[118] However, it should be borne in mind that the establishment of embryonic stem cell lines from cloned animal embryos is currently very inefficient (less than 5%) and the derivation of embryonic stem cells from a cloned human embryo has, as yet, proved elusive.

115 Byrne JA, Simonsson S, Western PS and Gurdon JB (2003) Nuclei of Adult Mammalian Somatic Cells Are Directly Reprogrammed to *oct-4* Stem Cells Gene Expression by Amphibian Oocytes. *Curr Biol* 13(14): 1206–1213.

116 Chen Y, He ZX, Liu A, Wang K, Mao WW, Chu JX, *et al*. (2003), Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes. *Cell Res* 13(4): 251–263.

117 Chang KH, Lim JM, Kang SK, Lee BC, Moon SY and Hwang WS (2003) Blastocyst formation, karyotype, and mitochondrial DNA of interspecies embryos derived from nuclear transfer of human cord fibroblasts into enucleated bovine oocytes. *Fertil Steril* 80(6): 1380–1387.

118 Advanced Cell Technology (1998) *Advanced Cell Technology Announces Use of Nuclear Transfer Technology for Successful Generation of Human Embryonic Stem Cells*. Press release, published 12 November 1998. Available online at: http://www.advancedcell.com/press-release/advanced-cell-technology-announces-use-of-nuclear-transfer-technology-for-successful-generation-of-human-embryonic-stem-cells, accessed 8 October 2007.

One area that may prove problematic in establishing embryonic stem cell lines from cytoplasmic human-animal hybrid embryos is proper mitochondrial functioning (generation of the energy necessary for cells to operate). The genetic material of a human-animal hybrid would be predominantly human but with some animal mtDNA from the enucleated animal egg used. Thus, unlike embryos created normally, which contain only maternally derived mtDNA (from the egg), cytoplasmic human-animal hybrids can possess mtDNA from either the human donor cell or the animal egg, or a combination of both (see Figure 4). Theoretically, this could interfere with mitochondrial gene and protein function in the newly formed human-animal hybrid, which in turn could affect the proper functioning of any cells derived from the embryo.[119]

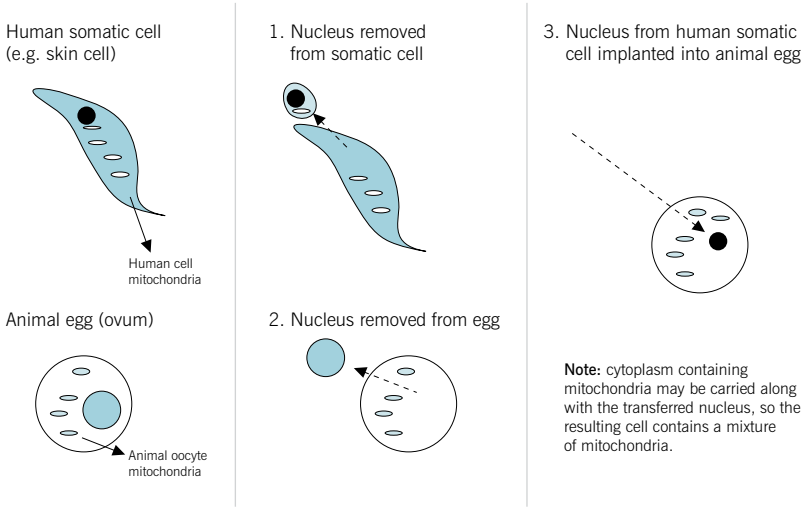

Figure 4. Creation of human-animal hybrid embryos.[120]

Furthermore, concerns have been raised in relation to the possibility of animal viruses being activated in cytoplasmic human-animal hybrids. The field of xenotransplantation (transplant of tissue or organs from one species to another) has highlighted the potential risk of infectious diseases from animal donors being spread to human recipients. In the context of cytoplasmic human-animal hybrid embryos, concerns exist that the mitochondria and cytoplasm from the animal egg represent potential pools of viruses.[121] The Academy of Medical Science in the United Kingdom (UK) has acknowledged that animal viruses could conceivably integrate into transferred human nuclei. However, given that researchers are not seeking to use cell lines derived from cytoplasmic human-animal hybrid embryos for treatment purposes for the time being, they do not consider this risk sufficient to justify banning the creation of such hybrid embryos for fundamental research purposes.[122]

119 St John J and Lovell-Badge R (2007) Human-animal cytoplasmic hybrid embryos, mitochondria, and an energetic debate. *Nat Cell Biol* 9(9): 988–992.

120 This figure was taken from the House of Commons Science and Technology Committee (2007) *Government proposals for the regulation of hybrid and chimera embryos. Fifth Report of Session 2006–07.* The Stationery Office Ltd., London. Parliamentary material is reproduced with the permission of the Controller of HMSO on behalf of Parliament.

121 Scottish Council on Human Bioethics. (2006) *Embryonic, Fetal and Post-natal Animal–Human Mixtures: An Ethical Discussion*. Edinburgh.

122 The Academy of Medical Sciences (2007) *op. cit*.

Alternative Sources of Embryonic Stem Cells

Given the moral concerns associated with the creation and destruction of human embryos, scientists are actively trying to develop alternative methods for obtaining embryonic or embryonic like stem cells, which do not involve the destruction of embryos. A brief presentation of the proposed alternative methods is provided below.

Dedifferentiation

Cell differentiation determines the role each cell in the body will play. It begins early in embryonic development and eventually leads cells to specialise into over 200 diverse cell types that form the human body. Cell differentiation also occurs in the fully developed adult body, *e.g.* adult stem cells differentiate to replace damaged cells. Dedifferentiation, also referred to as cellular "reprogramming", is the opposite process, during which specialised, differentiated cells revert to a less differentiated state. Dedifferentiated cells are then able to embark on a very different cell differentiation path than that from which they originated.

There is considerable research interest in exploiting cell dedifferentiation to reprogramme normal somatic cells to an embryonic like state. Cloning by SCNT effectively uses an enucleated egg to reprogramme the nucleus of a somatic cell. The mixture of "egg and somatic DNA" gains the totipotency of a zygote once an electrical or chemical stimulation is delivered to the system. Three different research laboratories in the US and Japan recently reported on another approach to reprogramming normal somatic cells so that they become stem cell like.[123,124,125] These research groups produced what they have termed "induced pluripotent stem cells" (iPS) from ordinary mouse skin cells (fibroblasts). They found that the expression of four proteins known to be important for development could coax these normal cells into an embryonic stem cell like state. In November 2007, two separate research teams from Japan[126] and the US[127] successfully applied this approach to human cells. The technique involved the introduction of three or four genes[128] known as transcription factors, into the fibroblasts, thereby reprogramming them to a pluripotent state. The cells were similar to embryonic stem cells in terms of their morphology, proliferation and differentiation potential. Expression of these factors associated with pluripotency increases the risk of tumour formation. In this regard, the most problematic of the transcription factors used for reprogramming (c-Myc, a gene associated with some forms of human cancer) can be eliminated from the reprogramming cocktail given to cells, albeit with a reduction in the efficiency of dedifferentiation.[129]

123 Okita K, Ichisaka T and Yamanaka S (2007) Generation of germline-competent induced pluripotent stem cells. *Nature* 448(7151): 313–317.

124 Wernig M, Meissner A, Foreman R, Brambrink T, Ku M, Hochedlinger K, *et al.* (2007) *In vitro* reprogramming of fibroblasts into a pluripotent ES-cell-like state. *Nature* 448(7151): 318–324.

125 Maherali N, Sridharan R, Xie W, Utikal J, Eminli S, Arnold K, Stadtfeld M, Yachechko R, Tchieu J, Jaenisch R, Plath K and Hochedlinger K (2007) Directly Reprogrammed Fibroblasts Show Global Epigenetic Remodeling and Widespread Tissue Contribution. *Cell Stem Cell* 1(1): 55–70.

126 Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K and Yamanaka S (2007) Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* 131(5): 861–872.

127 Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, *et al.* (2007) Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells. *Science* 318(5858): 1917–1920.

128 The Japanese team used the same four genes they had previously used to reprogramme mouse cells: OCT3/4, SOX2, KLF4 and c-MYC. The American team also used OCT3 and SOX2 as well as two different genes, NANOG and LIN28 in order to induce pluripotency in adult fibroblast cells.

129 Nakagawa M, Koyanagi M, Tanabe K, Takahashi K, Ichisaka T, Aoi T, *et al.* (2007) Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. *Nat Biotechnol* 26(1): 101–106.

In February 2008, Lowry *et al*. repeated the successful generation of iPS cells from human fibroblasts using the same combination of factors used by the Japanese team.[130] More recently, Park *et al.* reported reprogramming human cells from various sources, foetal, non foetal, as well as cells isolated from a skin biopsy of an adult volunteer.[131] Previous groups had produced iPS cells using commercially available cell lines. This work demonstrates it is feasible to obtain cells directly from volunteers for dedifferentiation.

Dedifferentiation holds considerable promise for generating patient and disease specific pluripotent stem cells that can be used to study genetic disease and possibly to develop stem cell based therapies in the future. The first proof-of-principle of therapeutic application in mice of iPS cells was reported in a sickle-cell anaemia mouse model in December 2007.[132]

However, these cells currently present significant technical challenges that must be overcome before they can be used in the treatment of patients. Our understanding of why the efficiency of dedifferentiation is so low is limited and only recently has any insight been gained with respect to the sequence of events, which occur during the dedifferentiation process in mice.[133,134] While this field is moving at a breathtaking pace, it will require time to examine the key question: whether iPS cells will differentiate as stably and diversely as embryonic stem cells. Furthermore, use of retroviruses to introduce the transcription factors into the adult cells to be dedifferentiated poses a significant safety concern. Retroviruses can introduce random disruptions into DNA, which can trigger tumour growth. Whether it will prove possible to dedifferentiate cells using non viral methods or non integrating viruses is yet to be determined but recent work in this area is promising. Aoi *et al.* recently reported that transcription factors do not need to be inserted into specific sites within the genome for liver and stomach cells to be dedifferentiated.[135] This opens the door to possibly getting the retrovirus to insert the transcription factors at places in the cells' DNA that are not associated with tumour growth. The authors have subsequently acknowledged that there were minor errors made in the paper and have successfully argued that these do not affect the central conclusions drawn.[136]

Given the current limits of our understanding of cell dedifferentiation, the process has yet to provide the research community with a sure and ethically uncontroversial supply of human pluripotent stem cells. Gaining a better understanding of the process will undoubtedly be of great value to stem cell research and to biological research in general. Nonetheless, in the short to medium term, it is unlikely that dedifferentiation will obviate the need for embryonic stem cells for research.[137]

130 Lowry WE, Richter L, Yachechko R, Pyle AD, Tchieu J, Sridharan R, *et al*. (2008) Generation of human induced pluripotent stem cells from dermal fibroblasts. *PNAS* 105(8): 2883–2888.

131 Park I-H, Zhao R, West JA, Yabuuchi A, Hongguang H, Ince TA, *et al*. (2008) Reprogramming of human somatic cells to pluripotency with defined factors. *Nature* 451(7175): 141–147.

132 Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, *et al*. (2007) Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. *Science* 318(5858): 1920–2923.

133 Brambrink T, Foreman R, Welstead GG, Lengner CJ, Wernig M, Suh H and Jaenisch R (2008) Sequential expression of pluripotency markers during reprogramming of mouse somatic cells. *Cell Stem Cell* 2(2): 151–159.

134 Stadtfeld M, Maherali N, Breault DT and Hochedlinger K (2008) Defining molecular cornerstones during fibroblast to iPS cell reprogramming in mouse. *Cell Stem Cell* 2(3): 1–11.

135 Aoi T, Kojiro Y, Nakagawa M, Ichisaka T, Okita K, Takahashi K, *et al*. (2008) Generation of Pluripotent Stem Cells from Adult Mouse Liver and Stomach Cells. *Science* doi:10.1126/science.1154884.

136 Editorial (2008) A reprogramming rush. *Nature* 452(7186): 388.

137 Hyun I, Hochedlinger K, Jaenisch R and Yamanaka S (2007) New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells. *Cell Stem Cell* 1(4): 367–368.

Single Blastomere Biopsy

Recently, researchers have used a technique modelled on preimplantation genetic diagnosis (PGD) to obtain human embryonic stem cells.[138] PGD involves removing one cell (called a blastomere) from an eight cell IVF embryo and looking at its DNA. This procedure is authorised by the UK Human Fertilisation and Embryology Authority (HFEA) so that couples who are carriers of serious genetic disease can select embryos that are not affected and, since 2004, can select embryos that are a tissue match for a sick sibling—sometimes referred to as "saviour siblings".

When the technique is adapted for the purposes of stem cell research, the single cell removed from an eight cell IVF embryo is used to establish an embryonic stem cell line rather than to carry out genetic tests. Experience with PGD indicates that this procedure would not lead to the destruction of the remaining seven cell embryo, which could potentially be used for infertility treatment. It was noted in the study that pioneered this method[139] that several blastomeres were taken from the embryos used and none of the embryos were allowed to develop beyond the end of the experiment. The researchers involved have since claimed to have repeated the procedure on an embryo that was then cryopreserved.[140] Additionally, the same team derived mouse embryonic stem cell lines from single cells removed from embryos at the eight cell stage and transferred the remaining seven cell embryos into surrogate mothers, in which they developed into normal mice.[141] Current data suggests that PGD is as safe as IVF for the developing embryo[142,143,144,145] but insight into potential long term health effects is still lacking.[146]

However, there is real concern that the cell removed from the embryo at this stage of development is still totipotent and might, therefore, have the capacity to form a viable human embryo on its own. Single cells isolated from rabbit and sheep embryos at the eight cell stage are capable of developing into normal rabbits and sheep.[147,148] It is unclear whether the same is true for human embryos, thus, destroying a single cell for the derivation of embryonic stem cells could be seen to be morally equivalent to destroying the entire eight cell embryo.

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138 Klimanskaya I, Chung Y, Becker S, Lu S-J and Lanza R (2006) Human embryonic stem cell lines derived from single blastomeres. *Nature* 444(7118): 481–485.

139 *ibid*.

140 Advanced Cell Technology (2007) *Advanced Cell Technology Develops First Human Embryonic Stem Cell Line without Destroying an Embryo.* Press release, published 21 June 2007. Available online at: http://www.advancedcell.com/press-release/advanced-cell-technology-develops-first-human-embryonic-stem-cell-line-without-destroying-an-embryo, accessed 25 June 2007.

141 Chung Y, Klimanskaya I, Becker S, Marh J, Lu S-J, Johnson J, *et al*. (2006) Embryonic and extraembryonic stem cell lines derived from single mouse blastomeres. *Nature* 439(7073): 216–219.

142 Handyside AH, Kontogianni EH, Hardy K and Winston RML (1990) Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. *Nature* 344(6268): 768–770.

143 Hardy K, Martin KL, Leese HJ, Winston RML and Handyside AH (1990) Human preimplantation development *in vitro* is not adversely affected by biopsy at the 8-cell stage. *Hum Reprod* 5(6): 708–714.

144 Staessen C, Platteau P, Van Assche E, Michiels A, Tournaye H, Camus M, *et al*. (2004) Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. *Hum Reprod* 19(12): 2849–2858.

145 Magli MC, Gianaroli L, Grieco N, Cefalù E, Ruvolo G and Ferraretti AP (2006) Cryopreservation of biopsied embryos at the blastocyst stage. *Hum Reprod* 21(10): 2656–2660.

146 Human Genetics Commission (2006) *Making Babies: reproductive decisions and genetic technologies*. London.

147 Moore NW, Adams CE and Rowson LE (1968) Developmental potential of single blastomeres of the rabbit egg. *J Reprod Fertil* 17(3): 527–531.

148 Willadsen SM (1981) The development capacity of blastomeres from 4- and 8-cell sheep embryos. *J Embryol Exp Morphol* 65: 165–172.

Non Viable Embryos

Many human embryonic stem cell lines have been established from IVF embryos that were not used for infertility treatment. Several of these stem cell lines were isolated from low grade embryos, which would not normally be transferred to the womb.[149] As discussed previously, a large proportion of IVF embryos exhibit varying degrees of abnormalities and many of these abnormalities will spontaneously arrest the embryos' development (see Figure 5). Research has shown that stem cells can be extracted from arrested, non viable IVF embryos and can be used to generate stable cell cultures.[150]

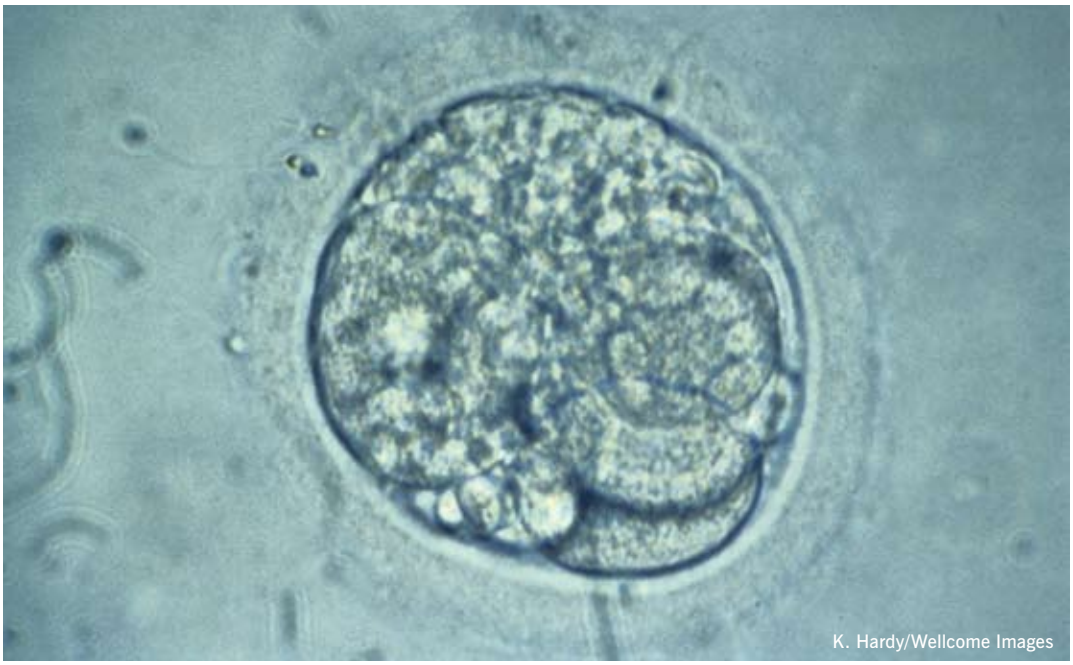

Figure 5. Non viable human embryo

Using arrested embryos, which will never reach the morula or blastocyst stage of embryonic development, would not normally be transferred to the IVF patient's womb and are generally regarded as "dead", may reduce the ethical concerns posed by destroying healthy (high grade) and viable human embryos.

An alternative to this approach is a variation of cloning called altered nuclear transfer (ANT). This method was proposed by William Hurlbut,[151] a member of the President's Council on Bioethics in the US, in an attempt to resolve, to some extent, the ethical problems associated with producing cloned human embryos to obtain patient specific embryonic stem cells.

149 Chen H, Qian K, Hu J, Liu D, Lu W, Yang Y, *et al.* (2005) The derivation of two additional human embryonic stem cell lines from day 3 embryos with low morphological scores. *Hum Reprod* 20(8): 2201–2206.

150 Zhang X, *et al.* (2006) *op. cit.*

151 Hurlbut WB (2005) Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells. *Perspect Biol Med* 48(2): 211–228.

In this technique, a gene necessary for embryo implantation is genetically modified in the donor nucleus before it is inserted into the egg *via* SCNT. The resulting embryo is, therefore, rendered genetically incapable of normal development. Proof of the principle of ANT has recently been established in mice.[152] Using a technique called RNA interference, researchers disrupted a gene called Cdx2, which enables an embryo to grow a placenta. With this gene effectively switched off, an embryo could not successfully implant in a uterus. Stem cells resulting from this procedure in the mouse model proved to be as robust and versatile as stem cells procured from mouse embryos in which the Cdx2 gene had not been interfered with.

Hurlburt asserts that, a human embryo created by ANT would be a biological entity "that lacks the attributes and capacity of the human embryo".[153] Thus, it could be argued that a potential human being is not destroyed once stem cells have been extracted from this embryo. However, it is unclear if Cdx2 is essential for placenta development in the human embryo and, as such, there is no guarantee that this procedure will always produce an embryo/entity incapable of normal development. Additionally, the genetic modification of embryos may have important consequences for any stem cells derived from them. Finally, the ethical acceptability of genetically modifying an embryo to ensure its non viability is highly contested.

Parthenogenesis

The term "parthenogenesis" is derived from the Greek for "virgin birth". It is an asexual form of reproduction in which females produce eggs, which develop without fertilisation. Certain insects, including bees and ants and some lizards can reproduce this way. Other species can resort to parthenogenesis if males are in short supply. A female hammerhead shark held in captivity at a zoo in Nebraska was recently shown to have given birth to a pup by parthenogenesis.[154]

Parthenogenesis can be artificially induced in mammals. However, mammalian parthenotes—the embryos that result from parthenogenesis—usually die after a few days of development. Parthenogenetic-normal chimeric embryos, in which some cells are parthenogenetic and the rest are normal, are an exception and can result in viable offspring. This phenomenon has been observed in humans.[155,156]

152 Meissner A and Jaenisch R (2006) Generation of nuclear transfer-derived pluripotent ES cells from cloned *Cdx2*-deficient blastocysts. *Nature* 439(7073): 212–215.

153 Hurlbut (2005) *op. cit.*

154 BBC News (2007) *Captive shark had 'virgin birth'*. BBC News, published online 23 May 2007. Available online at: http://news.bbc.co.uk/go/pr/fr/-/2/hi/science/nature/6681793.stm, accessed 20 June 2007.

155 Chimerism is described in the previous section "Human-Animal Hybrids".

156 Strain L, Warner JP, Johnston T and Bonthron DT (1995) A human parthenogenetic chimaera. *Nat Genet* 11(2): 164–169.

Genuine human parthenotes, which are unable to fully develop, have been artificially induced; and one research team managed, with much difficulty, to get them to develop to the blastocyst stage of embryonic development.[157,158] Stem cells taken from one of these embryos survived for a few days. In non human primates, stem cell lines have successfully been established from parthenotes.[159,160]

Parthenogenesis may prove to be a valuable approach to generating patient specific embryonic stem cells for female patients, because the prospective patient could potentially supply the eggs needed to create the parthenote. However, similarly to cloning, the technique remains highly inefficient. European leaders in the field, based at the Roslin Institute, reported in 2005 that it had taken 300 eggs to obtain half a dozen human parthenotes, which did not develop to a stage at which stem cells could be harvested.[161]

157 Rogers NT, Hobson E, Pickering S, Lai FA, Braude P and Swann K (2004) Phospholipase Cζ causes Ca^{2+} oscillations and parthenogenetic activation of human oocytes. *Reproduction* 128(6): 697–702. Roger NT, Hobson E, Pickering S, Lai FA, Braude P and Swann K (2005) Erratum: Phospholipase Cζ causes Ca^{2+} oscillations and parthenogenetic activation of human oocytes. *Reproduction* 129(1): 128.

158 Lin H, Lei J, Wininger D, Nguyen M-T, Khanna R, Hartmann C, *et al*. (2003) Multilineage Potential of Homozygous Stem Cells Derived from Metaphase II Oocytes. *Stem Cells* 21(2): 152–161.

159 Cibelli JB, Grant KA, Chapman KB, Cunniff K, Worst T, Green HL, *et al*. (2002) Parthenogenetic Stem Cells in Nonhuman Primates. *Science* 295(5556): 819.

160 Vrana KE, Hipp JD, Goss AM, McCool BA, Riddle DR, Walker SJ, *et al*. (2003) Nonhuman primate parthenogenetic stem cells. *PNAS* 100 (Supplement 1): 11911–11916.

161 Amos J (2005) *'Virgin conception' first for UK*. BBC News published online 9 September 2005. Available online at: http://news.bbc.co.uk/go/pr/fr/-/2/hi/science/nature/4228992.stm, accessed 21 June 2007.

ETHICAL CONSIDERATIONS

Non Embryonic Stem Cell Research

The ethical issues raised by the use of adult, umbilical cord and amniotic stem cells in research are comparable to those raised by the use of other human biological material in research. These issues have been addressed in detail in the Irish Council for Bioethics report *Human Biological Material: Recommendations for Collection, Use and Storage in Research* (2005) and will, therefore, not be covered in any depth here. One issue relating to adult stem cell research that does raise specific ethical questions is the collection and storage of umbilical cord stem cells and this issue is addressed in the section entitled Related Ethical Issues.

Valuable research with adult stem cells is currently being conducted in Ireland and elsewhere that is yielding significant scientific results and that may, in the future, lead to therapies in a number of disease areas. The Council supports this research once it is conducted in accordance with relevant legislation, scientific protocols and ethical guidelines.

Embryonic Stem Cell Research

Moral Status of the Embryo

Embryonic stem cell research raises serious ethical considerations because it, ultimately, depends on the use of human embryos as a source of stem cells and, consequently, on the destruction of the embryos. As such, assessments of the acceptability of this type of research are usually closely related to views of the moral status of the embryo.

In general terms, moral status defines the moral value that we accord to the various beings we share the world with, essentially, fellow humans and other animal species. When considering embryos, moral status refers to the moral value they are or ought to be accorded and furthermore, to the rights, if any, which are associated with this moral status. The moral status an individual would personally attribute to embryos is, therefore, likely to determine the level of legal protection that individuals would envisage granting them and is at the core of the ethical debate relating to stem cell research.

A range of positions can be taken with respect to the moral status of embryos. At one end of the spectrum, is the view that embryos are balls of cells that have no more moral value than any other piece of human biological material. At the other end, some would consider embryos to have the same moral status as any adult. This is the view that embryos have "full" moral status from the moment fertilisation is complete. Others grant significant value to early embryos but not the same status as they would grant to an adult. In this view, embryos will acquire full moral status at a later point during embryonic development.

In the view that embryonic life must be preserved from the moment fertilisation is complete, it is implied that embryos have an absolute right to life, which cannot be violated at any cost. Proponents of this view would object to current AHR practices because many of the embryos produced through IVF will not be used and, as such, will never develop and are, therefore, denied their right to life. The use of several types of contraception, such as intra-uterine devices and the "morning after pill", for example, can lead to the destruction of embryos in their earliest stages of development. Thus, their use also violates this ethical position. It is often argued that, given that human development is continuous from fertilisation to birth, any point at which full moral status were to be granted, other than at fertilisation, would necessarily be arbitrary and, therefore, unsound.

The Vatican instruction on human procreation adopts this view. The Roman Catholic tradition accords particular attention to the sanctity of human life and considers that embryos have the same intrinsic value as any fully developed human being. Embryos are simply the earliest stages of human existence and should be afforded full moral status.[162] Other religious communities, including many Protestant churches and Eastern Orthodox Christians, also take this view.

However, others have argued that the acquisition of moral status is as continuous a process as biological development and that embryos gradually gain their moral value. This is referred to as a gradualist view of moral status. Within this broad ethical position, some people do not think that there is a single point at which full moral status can clearly be attributed to the embryo. Where research on embryos is considered, it is argued that the relative moral value of the embryo should be considered in the context of the other values that can be realised through stem cell research in order to decide whether or not to proceed with it.

Alternatively, many people holding a gradualist view of moral status think that there are indeed criteria that allow additional moral status to be assigned at specific times during the course of embryonic development, even though the exact points at which this occurs will necessarily be, to a certain degree, arbitrary. Plato discussed this view in his presentation of "the fallacy of the beard". One might argue that there is no sharp distinction between a clean shaven man and a man with a full beard because at every point in between the two there is the tiniest increment of length of hair. In Plato's view, this argument is weak and there is a discernable difference between the two states of clean shaven and bearded. Plato, therefore, suggests that we should be able to make reasonable judgments to delimit stages or phases within continuous processes.

Indeed, for many centuries the Christian churches held a gradualist view of embryonic development. Thus, in the mid 19th century, the writings of the 13th century Christian theologian Thomas Aquinas on the question of embryonic development were still widely influential. Drawing on Aristotle, Aquinas considered that the human embryo did not possess a rational soul and was not a human being until 40 days of development in the case of males and 90 in the case of females. This view drew on an earlier distinction made by Aristotle between the "formed" and the "unformed" foetus. Aristotle recognised "quickening" (the point at which the mother first noticed foetal movements) as the point at which the human life began—when the foetus became animated with a human, rational soul.

162 Doerflinger RM (1999) The Ethics of Funding Embryonic Stem Cell Research: A Catholic Viewpoint. *Kennedy Inst Ethics J* 9(2): 137–150.

Aquinas adhered to the distinction between formed and unformed foetuses and the interpretation that only formed foetuses could be ensouled. The Penitentials (seventh century books of penance) graded the level of penance of abortion based on whether the foetus was formed or unformed. The same dictinction was reiterated in Roman Catholic Canon Law, which, from 1591 to 1869, imposed excommunication only for abortions of formed foetuses. This view has been interpreted as a gradualist position, which considers ensoulment as one of the critical events determining moral status. In the wake of a series of scientific discoveries in the 17th century and of a re-evaluation of earlier Christian theology, Pope Pius *IX*, in 1869, dropped the distinction between the *foetus animatus* and *foetus inanimatus*, giving support to the view that the soul is present in the embryo from conception, thereby granting full moral status to embryos from the moment fertilisation is complete.[163]

Similarly, the discussion of the moral and legal status of the embryo has evolved historically in Islamic jurisprudence, in accordance with science and technology. A satisfactory consensus encompassing the various Muslim schools of thought has not yet been reached, however, several presentations of Muslim views of embryonic stem cell research may provide guidance. In a submission made to the European Group on Ethics in Science and New Technologies (EGE), Sadek Beloucif emphasises that medical progress is highly valued in Islam: "scientific work is valued in Islam and considered an expression of adoration" and he explains that for most Muslim scholars, ensoulment occurs after 40 days of development.[164] According to Abdulaziz Sachedina,[165] the silence of the Koran over the particular point at which ensoulment occurs allows the distinction between a biological and a moral person to be made.

Just as the theological category of ensoulment can be considered to grant moral status, several developmental events, which occur during the normal course of embryogenesis, have also been put forward as defining moments at which embryos should acquire additional or full moral status. One such event is the implantation of the embryo into the mother's womb. This is widely considered to determine the onset of pregnancy and can be seen as a critical step in the establishment of a life.[166] Although differences in views exist within Judaism, this position appears to have emerged as the consensus among Jewish scholars.[167] It is accepted that if artificial wombs are developed and embryos no longer require a woman's body in order to develop, the question will have to be reviewed.

163 The contention that up until 1869 the human embryo had been considered to possess only a relative moral value has been contested. *The Didache*, an early second century Christian treatise, universally characterised abortion as homicide. Tertullian, an ecclesiastical writer in the second and third centuries, expressed the view in his *Apologia* that "to deny birth is to hasten homicide". St. Basil the Great considered that no significant distinction could be made between the formed and unformed foetus, a view later reflected by some Christians in the middle ages. Despite considering the unformed embryo as not fully human, it was believed that the embryo should not be attacked deliberately. Abortion of an unformed foetus was regarded as a different sin than abortion of a formed foetus; nonetheless, it was regarded as a grave sin and viewed as homicide in intent.

164 Beloucif S (2000) The Muslim's perspective related to stem cell research, in the European Group on Ethics in Science and New Technologies (2000) *Adoption of an Opinion on Ethical Aspects of Human Stem Cell Research and Use*. Brussels, p.119–123.

165 Sachedina A (2000) Islamic Perspectives on Research with Human Embryonic Stem Cells. Testimony of Abdulaziz Sachedina, Ph.D. University of Virginia. In the National Bioethics Advisory Commission (2000) *Ethical Issues in Human Stem Cell Research. Volume III, Religious Perspectives*. Rockville, Maryland, p.G-1-G-6.

166 The implantation of the embryo into the endometrial lining of the uterus is a process that usually occurs 8–12 days after the completion of fertilisation.

167 Union of Orthodox Jewish Congregations of America and the Rabbinical Council of America (2001) *Letter to President George W. Bush*. Available online at: http://www.ou.org/public/statements/2001/nate34.htm, accessed 31 August 2007.

The onset of the embryonic primitive streak, a phenomenon that occurs about 14 days after fertilisation, has also been proposed as a defining moment of development that is relevant to moral status. The reason for this judgment is that the primitive streak orients the early embryo and is the first definite and visible sign that it has begun gastrulation. Gastrulation is the process whereby embryonic cells begin to differentiate into categories of cells with specific fates. Furthermore, by the time the primitive streak appears, twinning will or will not have occurred. That the possibility of twinning has passed is considered by many to be important for moral status. This is because it is then possible to speak of a unique individual, rather than of an entity, which may or may not become two or more separate embryos. Along similar lines, some philosophers have argued that when a fertilised egg divides, such as when any other cell divides, it ceases to exist and is replaced by two new cells. They argue that, there is no individual which persists throughout these divisions and that only when the cells of an embryo begin to function as an organism, in a co-ordinated manner, does an embryo gain individuality.[168]

The view that as gastrulation begins, embryos acquire greater moral status, has been adopted by jurisdictions where research is allowed on embryos until 14 days of development. In Ireland, this position was recommended by the Commission on Assisted Human Reproduction (CAHR) in relation to allowing research on supernumerary IVF embryos.[169] Although additional moral value is clearly attributed after the primitive streak has appeared, it is worth noting that many of the jurisdictions upholding this view do not go as far as granting full moral status to embryos after this point.

Several other early embryonic events have been associated with the acquisition of additional moral status due to biological and physiological changes. These include the time at which neural tube development begins (around 18 days of development) and the onset of the foetal heartbeat about 22 days after fertilisation.

Within Christian theology, there are other strands of thought that are significant here, *e.g.* the relational school of theology stresses the importance of considering factors other than biological in considering when moral status is due. This school of thought bases its argument on the centrality of acceptance and recognition by the parents of the existence of a new life.[170] Parents, by their acceptance of the foetus, most often by naming it, confer the foetus with status. This school of thought holds that the foetus does not have full moral value until the decision of the parents to anticipate the human form and begin to speak of it as a human subject. Bruno Ribes has argued that in the absence of a relationship between the foetus and the parents, questions arise in relation to the legitimacy of allowing such a foetus to be born.[171]

Many scholars also consider that embryos acquire full moral status at a later point of embryonic development and they refer to the sensation of pain and/or pleasure, or to mental capacities, as critical elements of moral status. This view associates moral status with the idea of a person, meaning an individual with feelings and, in some views, thoughts.

168 McMahan J (1999) Cloning, killing and identity. *J Med Ethics* 25(2): 77–86.

169 The Commission on Assisted Human Reproduction (2005) *op. cit.*

170 Beinart L (1970) L'avoryement est-il infanticide? *Études*, vol. CCCXXXIII, p.522.

171 Smith D (1996) *Life and Morality: Contemporary Medico-moral Issues*. Gill and Macmillan, Dublin, p.34.

Personhood

The concept of personhood is commonly referred to in relation to moral status. For those who think full moral status should be limited to persons, the term is used to discuss the conditions necessary to acquire the status of a "person".

Whilst personhood may be a useful concept for the discussion of moral status, it has proven difficult to define and its conditions, which are taken to confer moral status, are highly controversial. There are, therefore, several different conceptions of personhood and its onset throughout human development. Traditionally, the conditions required for personhood have been broken down to include at least two capacities: one for rationality and the other for self consciousness.[172] Both of these capacities necessitate a certain level of brain function and it has been argued that they cannot accurately be measured and, therefore, are not good criteria for discerning moral status.

Philosophers concerned with human and animal rights have argued that the definition of personhood should be extended to include infants, the severely mentally impaired and some mammals. This position is supported by the fact that although severely mentally incapacitated individuals may lack rationality and/or self awareness, they are widely considered to be persons and are attributed full moral status in society. This view requires that a weaker version of rationality be used as a prerequisite for personhood. Some authors, such as the animal rights supporter Peter Singer, have gone as far as suggesting that personhood should be granted to all sentient beings.[173] Sentience can be defined as the capacity to react to external stimuli and to feel pleasure and/or pain. Plants and even machines, can react to stimuli but they cannot feel pleasure and/or pain. On the other hand, many animals are undoubtedly sentient by this measure and would, therefore, qualify as persons under this definition of personhood.

Even in this wider sense, early human embryos—such as those used to derive embryonic stem cells—do not qualify for personhood because the earliest time at which embryos could be considered sentient is set around the eighth week of development. This time point has been disputed, with many considering the onset of sentience to be much later, however, it is clear that embryos at the blastocyst stage (five-to-six days old) lack the minimum criterion necessary to qualify for this definition of personhood.[174] Even though it can be argued that the embryos under consideration in this report do not qualify for personhood and, by extension, do not possess full moral status, it is the view of the Council that qualifying for personhood is not necessary for the attribution of moral status or moral value to the embryo.

172 This is referred to as the Lockean definition of personhood, after the English philosopher John Locke's account of personhood in *An essay concerning human understanding* (1690).

173 Singer P (1990) *Animal Liberation*. New York Review Books, New York.

174 Current techniques establish embryonic stem cell lines by extracting cells from five to six day old blastocysts, which are destroyed by the process.

It has, nevertheless, been argued that human embryos are persons from the moment fertilisation has occurred or that personhood begins with the embryo.[175] The view that personhood should be attributed to all humans, regardless of their properties or capacities and/or in view of their potential to develop, is closely related to the "potentiality argument" discussed below. In this view, destroying an embryo is akin to killing a person and, by extension, experimenting on embryos is equivalent to experimenting on vulnerable populations without their consent. Following this reasoning, it has often been claimed that embryonic stem cell research is comparable to the Nazi medical experiments carried out in concentration camps during the Second World War.[176]

Potentiality

In discussing the moral status of embryos, various commentators refer to what can be called the "potentiality argument". The view is often expressed that embryos are due considerable moral status because they are "part of the human family" or "one of us". Such expressions suggest that, even if embryos do not qualify for personhood, their moral status should be considered in light of their potential to develop into fully fledged persons. These expressions also imply that there is something intrinsically special about human life.

Regarding the potential of embryos to develop, it is certainly true that an embryo is a nascent human life, which in the normal course of events will grow and may lead to the existence of a person.[177] Conversely, every human being was once a developing embryo.[178] Nevertheless, the potential that embryos possess fails to convince many scholars that they should be treated as persons. It is argued that there is a serious logical flaw in according rights to individuals based on their potential. For example, many of us have the potential to become criminals, yet it would not be considered reasonable to treat us as such unless we actually fulfil that potential. Such analogies can be criticised on the grounds that an embryo's potential is quite different from the potential individuals have to change their moral standing through their actions. The potential an embryo has is more basic: it is the potential to continue to exist and possibly develop into a person. However, the analogy does illustrate that moral rights are generally grounded in the actual, not potential, properties of a being.[179]

As previously discussed, fertilised eggs and early embryos are reported to have a high attrition rate (*i.e.* many of them die). This is considered by many to undermine the claim that all embryos have the potential to develop and, therefore, to weaken the potentiality argument. In other words, because many embryos will never develop, their potential and, by extension, the potentiality argument, is not decisive as a moral argument. Some philosophers have also drawn a distinction between the potentiality of

175 This was referred to as a transcendental, as opposed to an empirical, understanding of personhood by the theologian Maureen Junker-Kenny at the conference *Ethics of Stem Cell Research in a European Context. Autonomy, personhood, dignity: the diversity of philosophical interpretations and of legal positions in Europe*. Organised by the Centre for Ageing, Neurosciences and the Humanities, in association with The Meath Foundation, 7 September 2007.

176 The view was repeatedly expressed in the public consultation accompanying this document that, embryonic stem cell research was akin to the experiments conducted, without consent, on those in Nazi concentrations camps during World War II; see Appendix A.

177 Depending on the age of the embryo, it could lead to one or several persons' existence.

178 The President's Council on Bioethics (2002) *Human Cloning and Human Dignity: An Ethical Enquiry*. Washington, DC.

179 Brock DW (2006) Is a consensus possible on stem cell research? Moral and political obstacles. *J Med Ethics* 32(1): 36–42.

IVF embryos and embryos in a woman's womb, referred to as embryos *in utero*.[180] The reasoning is that embryos *in utero* have the potential to develop if left alone, whereas embryos *in vitro* cannot develop into mature human beings without considerable external interventions. It is argued that, the potential of embryos *in vitro*, in this context, is actually to perish.

The allusion to the special value of human life contained in expressions such as "embryos are part of the human family" has been the subject of much consideration. Some philosophers have claimed that this attitude is discriminatory towards members of other animal species and has even been termed "speciesism", by analogy with racism and sexism.[181] Others have attributed this phenomenon to the symbolic value of embryos, *i.e.* to the fact that they represent human life. Symbolic value explains why some individuals behave reverently towards flags, for example. Depending on one's point of view, symbolic value can be taken to warrant everything from a minor degree of respect to considerable moral status.

Human Dignity

The concept of human dignity is often appealed to in bioethics and has been widely integrated into human rights documents. Indeed, Article 1 of the *Charter of Fundamental Rights of the European Union* (2000) states that, "Human dignity is inviolable".

A major difficulty with the notion of human dignity is that it is often employed to justify both sides of a particular debate, which indicates that its exact meaning is elusive. This has been appropriately captured by Adam Schulman's introduction to a working paper submitted to the President's Council on Bioethics in the US:

> Human dignity—is it a useful concept in bioethics, one that sheds important light on the whole range of bioethical issues, from embryo research and assisted reproduction, to biomedical enhancement, to care of the disabled and the dying? Or is it, on the contrary, a useless concept—at best a vague substitute for other, more precise notions, at worst a mere slogan that camouflages unconvincing arguments and unarticulated biases?[182]

Schulman reviews the historical evolution of the term, from its original meaning in Greek and Roman antiquity of being worthy of honour and esteem, to its modern usage, which alludes to something fundamental that all humans possess. Biblical sources contributed significantly to the development of a shared notion of human dignity. In particular, the teaching that man is "made in the image of God", though elaborated in different ways in Jewish and Christian scripture, contains the message that there is something God like about Man that entitles humans to an "inherent and inalienable dignity". The influential 18th century philosopher Immanuel Kant defined a conception of human dignity, which demands equal respect for all persons based on their capacity for rational autonomy (ability to

180 Mahowald MB (2004) Respect for Embryos and the Potentiality Argument. *Theor Med Bioeth* 25(3): 209–214.

181 Ryder R (2005) All beings that feel pain deserve human rights. *The Guardian*, 6 August 2005. Available online at: http://www.guardian.co.uk/print/0,,5256582–110650,00.html, accessed 5 February 2008.

182 Schulman A (2005) *Bioethics and Human Dignity*. The President's Council on Bioethics Staff Working Paper. Available online at: http://bioethicsprint.bioethics.gov/background/human _ dignity.html, accessed 4 April 2007.

make decisions/take actions based on one's own genuine convictions and free from external influence). Kant's conception forbids the use of persons merely as a means to another person's ends. This prohibition of the "instrumentalisation" of human subjects is widely referred to in bioethical debates.

Following the atrocities of the Second World War, the concept of human dignity found its way into many 20th century declarations and constitutions, beginning with the *Charter of the United Nations* (1945). Schulman explains that the use of human dignity in this context most likely reflected a political consensus among parties, which may well have held very different views of the theoretical grounds for human dignity. The term was used to signify "whatever it is about human beings that entitles them to basic human rights and freedoms" and it was claimed to be inviolable in an attempt to avoid the reoccurrence of horrors such as forced labour and genocide.[183] *The Universal Declaration of Human Rights* (1948) also refers to "the inherent dignity…of all members of the human family".

Schulman concludes that, human dignity should be understood as our essential and inviolable humanity. What it is exactly that constitutes this humanity, however, remains to be defined. Agreeing on which elements of our humanity we value, consider essential and inviolable and, therefore, wish to protect, is at the heart of the question concerning the acceptability of embryonic stem cell research.

As discussed above, the moral status of the embryo can be discussed as an absolute, *i.e.* an "on/off" situation, or it can be seen in gradual terms. In the latter case, the moral value of the embryo is not necessarily equivalent to possessing full moral status and may be balanced against other values. Similarly, when it comes to determining those elements of our humanity that we value, there will, undoubtedly, be some that we consider absolutely inviolable and others which are seen to be valuable, yet can at times be balanced against other interests.

On consideration of the various arguments relating to the moral status of the embryo, the Council adopts a gradualist position, granting significant moral value rather than full moral status to human embryos. The moral value they are seen to possess is based on recognition of their potential to develop into persons, as well as the value they derive from representing human life in its earliest stages.

The Use of Supernumerary IVF Embryos for Embryonic Stem Cell Research

In its current state, AHR leads to the production of IVF embryos that, for many reasons, including the completion of a family or separation from a partner, may not all be used to achieve a pregnancy. There are four possible fates for these supernumerary embryos, which are not used by the individuals who produced them for AHR: they can be frozen and stored for an indefinite period or for a future pregnancy attempt; donated to another infertile woman; donated for use in research; or allowed to perish. It has been argued that all of the embryos produced for AHR should be given the chance to develop into a child. In Italy, women undergoing infertility treatment are required by law to allow all

183 Shultziner D (2003) Human Dignity—Functions and Meanings. *Global Jurist Topics* 3(3): Article 3.

of the embryos produced to be transferred to their wombs. Alternatively, the embryos could be donated to others who are not able to produce their own. However, patient surveys and experience in the field of infertility treatment indicate that many couples are not willing to donate their supernumerary embryos for someone else's parental project. In one study in the US, only 22% of individuals said they were somewhat or very likely to donate their remaining embryos for a projected pregnancy.[184] In a Danish study of 284 couples who had frozen embryos following IVF, more than half of these patients agreed to the concept of donation of supernumerary embryos for research, whereas less than one third agreed to donation to other infertile couples.[185] The data from this study led the authors to suggest that the more reluctant attitude towards embryo donation to other infertile couples than to medical research is, in large part, due to an aversion on behalf of a couple to the thought of other people raising their biological child/children. Qualitative data has demonstrated that there is a great deal of complexity inherent in decisions couples make in relation to the fate of their supernumerary embryos. Findings from studies conducted immediately prior to IVF treatment reveal a willingness on behalf of couples to donate their embryos.[186,187] This is largely driven by an altruistic wish to help other infertile couples. However, a number of studies conducted post IVF treatment consistently find that lower numbers of couples, ultimately, choose to donate their embryos and, where it is legal to do so, the great majority choose to dispose of them.[188,189] Data suggests that this change of mind is primarily driven by a change in perspective of the previously childless couple, who are now parents and who view an embryo as a "virtual child" rather than as an opportunity for pregnancy.[190] As such, embryo donation is equated with relinquishing a child to an unknown and uncertain future.

A key issue under consideration in the current Opinion document is whether it is acceptable in Ireland to use supernumerary IVF embryos, which would otherwise be destroyed or stored indefinitely, as a source of embryonic stem cells for research.

Acts and Omissions

The question of whether allowing supernumerary IVF embryos to perish is morally equivalent to actively destroying them for research purposes has generated considerable philosophical debate. It has been argued that there is a moral difference between acts and omissions: between actively killing something and passively failing to intervene to stop its death. Despite the fact that the outcome is the same in both cases, the view has been expressed that there is something more morally objectionable about actively bringing about a death. Alternatively, it has been argued that a decision not to do something is as much a decision as one to do something.[191] James Rachels uses the

184 Lyerly AD and Faden RR (2007) Willingness to Donate Frozen Embryos for Stem Cell Research. *Science* 317(5834): 46–47.

185 Bangsbøll S, Pinborg A, Yding Andersen C and Nyboe Andersen A (2004) Patients' attitudes towards donation of surplus cryopreserved embryos for treatment or research. *Hum Reprod* 19(10): 2415–2419.

186 Laruelle C and Englert Y (1995) Psychological study of in vitro fertilization-embryo transfer participants' attitudes toward the destiny of their supernumerary embryos. *Fertil Steril* 63(5): 1047–1050.

187 Lornage J, Chorier H, Boulieu D, Mathieu C and Czyba JC (1995) Six year follow-up of cryopreserved human embryos. *Hum Reprod* 10(10): 2610–2616.

188 Kovacs GT, Breheny SA and Dear MJ (2003) Embryo donation at an Australian university in-vitro fertilisation clinic: issues and outcomes. *Med J Aust* 178(3): 127–129.

189 Klock SC, Sheinin S and Kazer RR (2001) The Disposition of Unused Frozen Embryos. *N Engl J Med* 345(1): 69–70.

190 de Lacey S (2005) Parent identity and 'virtual' children: why patients discard rather than donate unused embryos. *Hum Reprod* 20(6): 1661–1669.

191 Singer P (1974) Philosophers are back on the job; The death of ethical and political argument was only temporary. *New York Times, Sunday Magazine*, 7 July 1974.

example of two men: Smith, who drowns his young cousin in a bathtub for his inheritance; and Jones, who plans to drown his young cousin but finds the boy already unconscious under water, as the result of an earlier fall and refrains from saving him.

In both cases the boy dies and Rachels concludes that there is no moral difference between killing and allowing to die—we are morally responsible for our actions, but also for our omissions or for what we fail to do when we could have reasonably acted otherwise.[192] The act–omission distinction is not particularly useful in discussing the fate of supernumerary embryos. Destruction of these embryos as a result of research certainly amounts to an "act" but so too does removal of supernumerary embryos from cold storage, which deprives them of the necessary conditions to secure their survival.

The "Nothing is Lost" Principle

The proposal to carry out research on supernumerary IVF embryos does not suggest that embryos should be destroyed merely for research purposes. Rather, if embryos are to be destroyed because they will not be used in a parental project, it is proposed that they be used for research, which also leads to their destruction, instead of simply being destroyed. The basis for this proposal is that nothing is lost, because the embryos will in fact either be destroyed or remain frozen and so will never be allowed to develop; but if they are used for research, something valuable may be gained, namely, advancement of scientific research.

Gene Outka defends such a position based on the "nothing is lost" principle. He argues that despite the fact that embryos do have moral value, if supernumerary embryos are not to be implanted then nothing is lost by their being used for embryonic stem cell research and, in fact, something might be gained.[193] The use of embryos for research determines how the embryo will die and not whether death will occur. The "nothing is lost" principle was developed by Paul Ramsey and attaches two exempting conditions to the prohibition against the intentional killing of an innocent life.[194] Ramsey argues that it may be justified to kill if the innocent will die in any case and if death will save other innocent lives. Outka extends this principle to the question at hand and argues that, it is correct to view supernumerary embryos as innocent lives that will be terminated in any case (by being discarded or frozen in perpetuity) and to regard third parties with diseases that could potentially benefit from stem cell research as innocent lives that could be saved as a result of the killing.

Critics of the "nothing is lost" principle argue that using supernumerary embryos for research is analogous to killing a doomed human being, *e.g.* a terminally ill patient, in order to benefit others.[195] However, this objection only holds true if one considers that embryos have full moral status.

192 Rachels J (1975) Active and passive euthanasia. *New Engl J Med* 292(2): 78–80.

193 Outka GH (2002) The Ethics of Human Stem Cell Research. *Kennedy Inst Ethics J* 12(2): 175–213.

194 Ramsey P (1961) *War and the Christian Conscience: How Shall Modern War Be Conducted Justly?* Duke University Press, Durham, NC, p.171–191.

195 Fletcher JC (2001) NBAC's Arguments on Embryo Research: Strengths and Weaknesses. In Holland S, Lebacqz K and Zoloth L (eds.) *The Human Embryonic Stem Cell Debate: Science, Ethics, and Public Policy*. MIT Press, Cambridge, MA, p.61–72.

Principle of Proportionality

As previously discussed, the Council considers that embryos produced in the context of infertility treatment should be attributed moral value rather than full moral status and they should, therefore, be treated with a level of respect that is commensurate with this value. According moral value rather than full moral status to embryos implies that it may be permissible to destroy these embryos in certain cases. In the debate about embryonic stem cell research, it has been pointed out that, respect for human life must also take into account those who are suffering from serious disease and would benefit from any medical advances stem cell research may offer. In other words, we value embryos, but we also value the welfare of patients and, thereby, we value medical progress.

From this perspective, the respect due to embryos should be balanced against the value that may be derived for all humanity through medical advances. Balancing the value of embryos against the value of patient welfare implies that destroying embryos for research requires a strong justification in terms of its expected benefits to patients. This might entail that the therapeutic potential of the research has to be reasonably demonstrated, that all of the alternative research methods have been exhausted and that the disease or condition that the medical research targets is life threatening. Such considerations relate to the principle of proportionality, which addresses situations in which values are in conflict. The principle acknowledges that it may not always be possible to satisfy all competing interests and, in such cases, the resolution should be proportionate to the competing values in question in order to be justified. The principle explains, for example, why it would not be considered acceptable to use embryos for research aimed at developing cosmetics because this goal is not regarded to be of particular moral value.

It can be argued that, at present, research on adult stem cells has yet to be exhausted and, therefore, using embryonic stem cells has not yet become a proportionate response to the needs of medical science. However, as discussed in the Scientific Aspects of Stem Cell Research section, scientists cannot currently predict with any degree of certainty whether adult or embryonic stem cells are more likely to be successful in the development of treatments for disease. Without research on both adult and embryonic stem cells, it is impossible to provide definitive evidence of which approach will be most successful. Yamanaka and his colleagues, who recently induced pluripotent stem cells from adult human fibroblasts, argue that this achievement would not have been possible without embryonic stem cell research, pointing out that knowledge from work with embryonic stem cells can cross pollinate with adult stem cell research and *vice versa*.[196] Further, those authors express the concern that "progress toward socially beneficial applications of stem cell science would be indefensibly delayed if induced pluripotent stem cell research is pursued at the expense of further human embryonic stem cell research". In the absence of definitive evidence that adult stem cells offer an equal or better prospect than embryonic stem cells for developing therapies, the Council considers embryonic stem cell research to be a proportionate response to the needs of medical research.

196 Hyun *et al*. (2007) *op. cit*.

The Council believes that, the moral value of human embryos that will otherwise remain frozen or be destroyed needs to be balanced against the moral value of human welfare, which is likely to increase with advances in medical science that ameliorate quality of life. While accepting the value of human life demands that we hold significant respect for embryos, it also demands that we consider our obligations to care for humankind more generally. The Council would, therefore, consider embryonic stem cell research to be acceptable in certain contexts. That is, the Council supports the carefully regulated use of supernumerary IVF embryos—that are otherwise destined to be destroyed—for the purposes of embryonic stem cell research aimed at alleviating human suffering. The decision to donate supernumerary embryos for research should be voluntary, free from any form of coercion and made under the strict conditions of informed consent.

Moral Complicity

If clinical treatments are developed from embryonic stem cell research, an ethical dilemma will arise for those who are opposed to the use of supernumerary embryos for such research: would it be morally acceptable to benefit from these treatments? Using a product of embryonic stem cell research can be seen as furthering a situation that is dependent on the destruction of embryos and even as a co-operation or collaboration with the research itself. Similar questions are raised when considering the importation of embryonic stem cell lines for research. Some countries, which do not allow the use of supernumerary embryos for stem cell research, have, nonetheless, allowed the importation of embryonic stem cell lines or the use of pre-established cell lines for research.

The principle of co-operation concerns the examination of how an action by an individual may contribute to an immoral act by another. In regard to co-operation, there is recognition that despite not being the primary agents of an act, we may play a role in the actions of others. There are several levels of co-operation, the first distinction that can be made in this regard is that between "formal" and "material" co-operation. In formal co-operation, one shares the intent of committing the evil and such formal co-operation is always considered morally illicit, regardless of the closeness of the involvement. According to this school of thought, if one gives support to derivation of embryonic stem cells from embryos, one is as morally culpable as the scientist who commits the act. In material co-operation, one shares the act but not the intent. If one becomes involved in an immoral act without having the same intention of the person performing the act, then one co-operates not formally but materially. A further distinction arises in the context of material co-operation. If someone contributes to the active performance of an immoral act in such a way that without that person's involvement the act could not be performed, this is considered to be "immediate material" co-operation (*e.g.* supply by fertility clinics of supernumerary embryos to scientists for derivation of stem cell lines). In "mediate material" co-operation one does not participate directly, but performs some indirect function that supports the occurrence of the act (*e.g.* use of therapies derived from embryonic stem cells/importation of embryonic stem cell lines). The view has been expressed that this form of

co-operation is not always illicit and under certain circumstances may be justified. For example, the good achieved by the mediate material co-operation must outweigh the degree of immoral activity. Furthermore, the contribution to the immoral act and the relative proximity or remoteness of that contribution to the immoral act is also weighed in determining its moral acceptability.[197]

The question of whether benefitting from others' wrongdoing effectively makes one a moral accomplice to the evil deed has also been discussed in the context of using research results from Nazi medical experiments.[198] The issue of a causal connection between the use of goods (therapies or stem cell lines) produced through evil and the encouragement of wrongdoing in the future is of particular relevance here. Ronald Green suggests that individuals who make use of such goods might directly encourage the commission of evil deeds through the acceptance of benefit.[199] If an evil deed is independently committed by an individual and, instead of foregoing the benefit of that deed, another individual enjoys the benefit and ignores the wrongdoing, this could encourage future transgressions. Conversely, it has been argued that the "no benefit from others' wrongdoing" theory of complicity is too broad to be practically useful. Such a view would make each one of us morally complicit in any immoral action, no matter how far removed we are from the original action, *e.g.* purchasing clothing from companies who manufacture their products in sweatshops.

Benefiting from the use of embryonic stem cell lines or therapies derived from research one does not support raises serious considerations about moral consistency. If one accepts that moral consistency is desirable, it would be necessary to support embryonic stem cell research in Ireland if individuals wish to avail of the medical products that may flow from the research. To fail to attain moral consistency is often seen to reflect a lack of moral courage and has been referred to as a "moral free ride". Nonetheless, it can be argued that moral consistency does not always lend itself well to practical policy solutions, especially when a plurality of opinion exists within society.

The issues of complicity and moral consistency are only relevant if one believes that the destruction of embryos is, without exception, immoral and one still wishes to avail of therapies or import embryonic stem cells for research. As the Council does not object to the derivation of embryonic stem cells from supernumerary IVF embryos, it has no objection to the use of therapies or importation of stem cells derived from embryos.

197 Ashley BM and O'Rourke KD (1997) *Health Care Ethics: A Theological Analysis*. Georgetown University Press, Washington DC, p.193–195.

198 Green RM (2002) Benefiting from 'Evil': An Incipient Moral Problem in Human Stem Cell Research. *Bioethics* 16(6): 544–556.

199 *ibid.*

The Creation of Embryos Specifically for Research Purposes

It is now possible to create embryos not only by fertilisation of an egg by sperm, but also by means of cloning (SCNT). The resulting embryos can be used for research purposes. Two questions arise in this context. First, are embryos created by IVF morally equivalent to those created by SCNT? Second, does an ethical distinction exist between the use of supernumerary IVF embryos for the derivation of embryonic stem cells and the use of embryos created specifically for this purpose?

Moral Equivalence of IVF and SCNT Embryos Created for Research

The potentiality argument has been used in part to support conferring moral value to the embryo. Although fertilisation of an egg with sperm *in vitro* clearly results in an embryo, which has the potential to develop into a human being if implanted into the uterus, it is less clear if an embryo created by SCNT possesses the same potential. While SCNT technology is highly inefficient in producing cloned mammals, animals such as sheep, cows and dogs have been successfully brought to term. In November 2007, scientists cloned embryos from a macaque, thereby, overcoming what was previously thought to be the insurmountable problem of cloning primates.[200] It is doubtful that definitive evidence of the potential of SCNT embryos to develop into human beings will be forthcoming, as the studies required to prove this thesis are not likely to be undertaken in light of the general objection to human reproductive cloning. The concept of genetic uniqueness has been used to argue that a moral difference exists between IVF embryos and those created by SCNT. The genetic component of a fertilised egg is unique, with a contribution of genetic material being made by both egg and sperm. This is not the case in SCNT, where the genetic content is identical to that of the donor who provided the nuclear material. Deriving human uniqueness from genetic uniqueness in order to morally differentiate IVF and SCNT embryos is not entirely persuasive, however, when one considers that identical twins have identical genomes.

The Council does not consider that a distinction should be made between the moral status of an IVF or an SCNT embryo. Thus, similar concerns regarding the creation of IVF embryos for research purposes apply to embryos created by SCNT. This view is based on evidence of the potential of animal SCNT embryos to develop into a variety of animals and on the uncertainty regarding the potential of human SCNT embryos to develop into human beings.

Instrumentalisation

In many countries, the destruction of supernumerary IVF embryos is not considered morally equivalent to the creation of embryos solely for the purpose of research—also referred to as "research embryos".

200 Byrne *et al.* (2007) *op. cit.*

One basis for the objection to the creation of embryos for research purposes is that to create embryos with the sole intention of using them in research is to treat them instrumentally, merely as a means to another's benefit, thus, reducing the status of the embryo to that of a mere commodity. This commodification can be objected to especially if one sympathises with Kant's prohibition of the instrumentalisation of human life, which forbids the use of human subjects merely as a means to another person's ends.[201] It should be noted, however, that as Kant formulated the restriction, it was an objection to using "rational beings" solely as a means for the benefit of others on the basis that their interests are harmed by treatment as a mere means.

The intention with which embryos are produced is important when it comes to assessing ethical acceptability. In the case of supernumerary IVF embryos, the reason for creating them is to implant them into the uterus in the hope of establishing a successful pregnancy. Unlike embryos created by IVF or SCNT with the sole purpose of producing embryonic stem cell lines, supernumerary embryos are not created merely as a means for research ends. Katrien Devolder is critical of this line of reasoning.[202] She argues that once we have accepted the creation and sacrifice of human embryos to benefit infertile patients, we cannot argue that the creation and sacrifice of embryos for research, which may benefit ill and injured people, is a very different situation. In both cases embryos are used as a means to alleviate human suffering and increase human well being.

Intrumentalisation calls into question the recognition and respect due to embryos as entities belonging to the human species. Embryos, even if not attributed full moral status, nonetheless, have intrinsic value: they are the beginnings of a possible human life and are, therefore, worthy of respect. As embryos are the first stage of a new human life, they are ordinarily created for the purpose of bringing a life into the world. Consequently, embryos can function as powerful symbols and can provide the opportunity for a society to express a view about the importance or value of human life. John Robertson argues that the creation of embryos specifically for research has the capacity to weaken our communal respect for human life.[203] The US National Bioethics Advisory Council (NBAC)— now the President's Council on Bioethics—articulated a similar view in its 1999 report: "An ethical intuition that seems to motivate the 'discarded–created' distinction is that the act of creating an embryo for reproduction is respectful in a way that is commensurate with the moral status of the embryo, while the act of creating an embryo for research is not".[204]

The Least Morally Offensive Approach

When differences in opinion and/or beliefs persist, an ethical obligation exists to seek the least contentious means of achieving benefits. If identical results can be obtained from two types of research, that which is the least offensive or morally problematic should be adopted.[205] If, for example, adult stem cells and embryonic stem cells currently offered exactly the same possibilities

201 Kant I (1785) *Groundwork of the Metaphysics of Morals*, translated by Paton HJ (1964). HarperCollins, New York.

202 Devolder K (2005) Creating and sacrificing embryos for stem cells. *J Med Ethics* 31(6): 366–370.

203 Robertson JA (1995) Symbolic Issues in Embryo Research. *Hastings Cent Rep* 25(1): 37–38.

204 National Bioethics Advisory Commission (1999) *Ethical Issues in Human Stem Cell Research. Volume I, Report and Recommendations of the National Bioethics Advisory Commission*. Rockville, Maryland, p.56.

205 Doerflinger (1999) *op.cit*.

and were equal in all other respects, *e.g.* ease of access, proliferation then research using adult stem cells would be preferred. As previously discussed, this is not currently the case. While the iPS cell approach circumvents many of the ethical concerns over the use of human embryos for research, the consensus of those scientists working with iPS cells is that further research comparing these dedifferentiated cells with stem cells from embryos, considered the gold standard, is necessary. If the technical challenges associated with iPS cells can be overcome and these cells prove to be as effective as embryonic stem cells in their potential to deliver therapies, iPS cells might well constitute the least morally offensive approach in the future.

Given the concerns relating to instrumentalisation, it can be argued that the least morally offensive approach supports a prohibition on the creation of embryos for research while supernumerary IVF embryos exist. This approach can only have merit if proof exists that research with supernumerary IVF embryos will achieve the same goals as embryos created solely for research purposes. While this holds for supernumerary IVF embryos and embryos created by IVF specifically for research, a distinction should be made in the case of SCNT embryos. It can be argued that SCNT embryos are equal and in fact superior to IVF embryos, as they offer the possibility of producing patient specific embryonic stem cells. However, it should be pointed out that human embryonic stem cells have yet to be successfully derived from a cloned embryo and the efficiency of cloning by SCNT is extremely low. Furthermore, Ian Wilmut, a man inextricably linked with SCNT cloning since the birth of Dolly the sheep a decade ago, has pointed out that the resources and time required to produce patient specific differentiated cells for large scale use is impractical.[206] In the case of supernumerary IVF embryos, the Council has taken the position that the embryo has moral value and that research resulting in the destruction of the embryo can only be justified if the potential benefits of the research to society are substantial. The potential benefits offered by SCNT embryos over and above those of supernumerary IVF embryos may be significant but remain speculative.

Egg Donation

Another objection to the creation of embryos for research is based on an issue of social justice, namely, the potential exploitation of emotionally and/or financially vulnerable women in egg procurement. These concerns were raised in the media when allegations were made that researcher Hwang Woo Suk, who led the team involved with the fraudulent cloning data, had coerced junior members of his laboratory into donating eggs for this research. It also emerged that he lied about the number of eggs that had been necessary for the experiments: apparently using over 2,000 donated human eggs, more than five times the amount reported in his publications. As previously discussed, egg procurement is an invasive procedure not without risk. These risks and, in many cases, the lack of direct benefit to women donating eggs for research, raise the question of why women would consent to such donation.

Currently, the primary source of eggs for research is through egg donation programmes run by fertility clinics, as there may be more eggs harvested than needed for infertility treatment. In the UK, programmes whereby women receive a discount from the cost of their IVF cycle if they donate eggs have been introduced. Ethical concerns have been raised with regard to these “egg sharing” schemes,

206 Wilmut I and Taylor J (2007) Stem cells: Primates join the club. *Nature* 450(7169): 485–486.

due to possible coercion of often emotionally vulnerable women, through financial incentives. The principal cause for concern is that compensation of egg donors could render their decision to donate coerced, or at least subject to undue influence, particularly in the case of the economically disadvantaged who are most likely to participate in egg sharing schemes. Such concerns are even more pertinent in the case of women who are not undergoing infertility treatment, often referred to as "altruistic" donors. Altruistic donors are placing themselves at risk during the egg harvesting process for no direct benefit to themselves and the financial compensations for such donors are likely to be quite substantial given the medical procedures involved. This has heightened the concern that the compensation policies offered could lead to the exploitation of the economically disadvantaged, who might be more willing to accept the risks involved for monetary gain. The US National Academy of Sciences is of the opinion that it would be difficult to justify recruiting altruistic egg donors among women who are not undergoing IVF treatment for their own reproductive purposes.[207] However, the HFEA in the UK agreed in February 2007 "to allow women to donate their eggs for research, either as an altruistic donor or in conjunction with their own IVF treatment".[208]

Paying women to donate their eggs has been discouraged on the grounds that it leads to the commercialisation of the human body by placing a monetary value on specific tissues and body parts. Such commercialisation could be viewed as serving to instrumentalise women as a source of raw materials for research. However, it should be noted that, research subjects are often paid for their involvement in drug trials, to compensate them for the time and effort invested in taking part in the research project. Therefore, it has been argued that women should be compensated for their time, travel and inconvenience, as well as for the risks undertaken during the egg harvesting procedure.[209]

It can be argued that, if sufficient safeguards are in place (*e.g.* research ethics review, counselling sessions), once fully informed, women should be allowed to voluntarily donate their eggs for research as an expression of their personal autonomy. If a woman has given such consent it may be inappropriate to consider her as being instrumentalised. In this respect, the accuracy and extent of the information provided as part of the consent process is vital. Prohibiting women from undertaking the risks inherent in egg donation could be considered to be overly paternalistic and inconsistent with practice in other areas of research. Reasonable limits to financial compensation, registration of all donors and limiting the number of cycles for donation may represent a possible means of addressing concerns relating to exploitation.

Cytoplasmic Human-Animal Hybrids

There is a possible solution to the problem of the shortage of human eggs, which would obviate the need to ask women to donate their eggs for research. Human-animal hybrid embryos have been suggested as an alternative source for the derivation of embryonic stem cells. It is possible that the creation of cytoplasmic human-animal hybrids, for the purpose of stem cell research, will be increasingly

207 Committee on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research, Giudice L, Santa E, Pool R, and the National Research Council (2007) *Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research: Workshop Report*. The National Academies Press, Washington, DC.

208 Human Fertilisation & Embryology Authority (2007) *HFEA Statement on Donating Eggs for research*. Press release, published 21 February 2007. Available online at: http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-EE78FF9E/hfea/hs.xsl/1491.html, accessed 22 June 2007.

209 Editorial (2006) Safeguards for donors. *Nature* 442(7103): 601.

applied in research into human diseases (in September 2007 the HFEA gave permission for such research to be carried out in the UK). Nevertheless, this technique has not been without opposition and a number of ethical concerns have been raised, not least of which is an inherent negative, guttural response to such entities.

The "Yuck" Factor

Human-animal hybrids have a long and rich cultural tradition. Much folklore, both Eastern and Western, contains stories of creatures that are half-man half-beast. In Indian mythology, for example, Ganesha had the body of a man and the head of an elephant. In ancient Greece, Minotaur was a man with the head of a bull and centaurs were creatures with the body, legs and tail of a horse and the torso, arms and head of a man. While in ancient Egypt, gods were represented as having the body of a man and the head of an animal, for instance, Anubis (god of the dead) had the head of a jackal.[210] Frequently, these creatures were depicted as symbols of waywardness, which were to be avoided or feared. Public opinion is often based on cultural values and it is, therefore, possible that traditional depictions of hybrids have led to their creation, for the purpose of stem cell research, meeting with significant opposition. This opposition, often referred to as the "yuck" factor, is generally based on an intuitive negative response to a practice, idea or thing.

The yuck factor or "wisdom of repugnance"[211] are very much linked to the phenomenon of moral taboos and are said to be legitimised by moral revulsions, which are held in common by all people in a society. For example, society considers cannibalism and incest to be morally taboo practices and is, therefore, instinctively opposed to them.[212]

The yuck factor, has been criticised for placing excessive value on emotion rather than rationality. It could be argued that, in the past, society has upheld taboos against practices that would now be considered to be perfectly ethical. For instance, blood transfusions, organ donation, certain ethnicities and homosexuality were all, at one time or another, regarded as repugnant by society. In the main, these views have been overturned. For example, blood donation is now deemed by most to be an ethical and civic responsibility.

Unnaturalness and Species Integrity

In relation to biotechnology specifically, the yuck factor often centres on the sense of something being unnatural. The natural element that is, in this instance, believed to be under threat is the concept of species integrity.

The philosophy of *telos*, also known as the "intrinsic value" or "integrity" of a being, was formulated by Aristotle and suggests that every living being has an innate tendency to reach its specific end or goal by displaying certain biological characteristics and undertaking particular functions. According to the unnaturalness argument, it would be wrong to change the nature of beings in ways that would

210 Deschamps J-Y, Roux FA, Saï P and Gouin E (2005) History of xenotransplantation. *Xenotransplantation* 12(2): 91–109.

211 Kass LR (1997) The Wisdom of Repugnance. *New Republic* 216(22): 17–26.

212 Karpowicz P, Cohen CB and van der Kooy D (2004) It is ethical to transplant human stem cells into nonhuman embryos. *Nat Med* 10(4): 331–335.

prevent them from following their natural course of development.[213] Therefore, natural law theorists argue that, combining human and animal tissues within embryonic entities thwarts the goals or ends of the beings involved and would, thus, be unnatural and immoral. Traditional teleological ideas about unnaturalness also criticise modern technologies, such as IVF and organ donation, which would appear to violate the natural functions of the individuals involved. However, it has been argued that these technologies allow human beings to perform two of their most basic natural functions, *i.e.* reproduction and survival.[214]

The species integrity argument assumes that current assessments of species are objective, infallible and ethically necessary.[215] However, there is much debate about whether species are real or merely the products of human methods of categorisation. It could be argued that the classification of species is experiential and that species categories have little meaning and carry insignificant moral weight.

Human Dignity

According to Immanuel Kant, who brought the concept of human dignity to the fore in Western philosophical thought, human beings have incomparable value because they are moral agents who are responsible for their own actions.[216] There have been suggestions that the production of human-animal hybrids, in which the lines between human and non human are blurred, could undermine the concept of human dignity.[217] There have been calls for a moral limit to be put on research involving the combination of human and animal materials, and these calls are based on concerns about how the resultant animals might threaten human dignity.[218] Concerns have also been raised that human-animal hybrids created at the embryo stage, if implanted and brought to term, would possess the same neurological and psychological behaviours as human beings and would, therefore, have the same claim to moral status, thus, disparaging human dignity. As was previously discussed in the section relating to the moral status of the embryo, one of the primary difficulties with human dignity as a concept is that its meaning is diffuse and has often been employed to justify both sides of a particular debate.

There are fears that human-animal hybrid embryos might be implanted and brought to term and questions have, therefore, been raised about how society might treat the resultant entities. In 1920s Soviet Union, Joseph Stalin ordered animal breeding scientist Il'ya Ivanov to attempt impregnating female chimpanzees with human sperm in order to create a human-chimpanzee hybrid, dubbed a "Humanzee". Stalin's aim was to create a strong yet disposable soldier race. The experiments were unsuccessful but were believed to be feasible by some leading scientists at the time. Due to a lack of funding, as well as the dangerous political climate that then existed in Russia, the research was

213 Kass LR (1985) *Towards a More Natural Science: Biology and Human Affairs*. Free Press, New York, p.249–275.

214 Karpowicz P, Cohen CB and van der Kooy D (2005) Developing Human-Nonhuman Chimeras in Human Stem Cell Research: Ethical Issues and Boundaries. *Kennedy Inst Ethics J* 15(2): 107–134.

215 Karpowicz *et al*. (2004) *op. cit.*

216 Kant (1785) *op. cit.*

217 Committee on Guidelines for Human Embryonic Stem Cell Research and the National Research Council (2005) *Guidelines for Human Embryonic Stem Cell Research*. The National Academies Press, Washington, DC, p.55.

218 The President's Council on Bioethics (2004b) *Reproduction and Responsibility: The Regulation of New Biotechnologies*. Washington, DC.

eventually abandoned.[219] While this is an extreme example of some of the feared abuses of human-animal hybrid research, a number of ethical concerns have been raised in relation to the "slippery slope" that might ensue following the creation of human-animal hybrids for stem cell research. For instance, there are fears that allowing the creation of human-animal hybrids *via* SCNT might lead to more radical research, such as fertilising the eggs of one species with the sperm of another.

Slippery Slope: the Possibility of Reproductive Cloning

In general, opposition to SCNT technology which can be used to create human embryos and human-animal hybrid embryos for research, not only reflects concerns over creating embryos solely for research purposes, it also results from societal and ethical concerns about the implications the technology could have in terms of human reproductive cloning. Cloning *via* SCNT makes reproductive cloning a possibility and critics commonly refer to what is called the "slippery slope". The slippery slope argument, as noted above, basically states that allowing one practice to occur now will inevitably result in another unwelcome practice being allowed in the future. Many opponents of SCNT would take the view that it is preferable to completely prevent the use of such technology, despite its potential benefits, than to facilitate the possibility for the emergence of reproductive cloning in the future. While the ethical implications of reproductive cloning lie outside the scope of this report, the widespread opposition to reproductive cloning is based on a number of concerns, including potential health risks for clones and threats to human diversity, identity and dignity.

Critics of the slippery slope argument have questioned its "alleged inevitability" and have argued that allowing one action will not necessarily result in another, less favoured, action being allowed or carried out in the future.[220] In this regard, it could be considered unacceptable to set boundaries for research, such as forbidding SCNT technology, on the basis that once it is allowed it could potentially result in abuses of this technology in the future, particularly given the practical, ethical and legal regulations that can be implemented to prevent abuses in research.

Notwithstanding these criticisms, the slippery slope argument is still considered significant, because it forces a "discussion of potential abuse of certain newly proposed moral boundaries".[221] Such deliberations can help identify specific problems or dangers with newly proposed research, technology or medical practices that might otherwise be overlooked.[222] With that in mind, it has been suggested that once the unwanted outcome of a particular scientific or medical technology has been identified, it should still be possible to allow the preferred uses of the technology, while prohibiting the unwelcome uses. This has been described as the ability to start down the slippery slope but to stop before problems arise.[223]

219 Rossiianov K (2002) Beyond Species: Il'ya Ivanov and His Experiments on Cross-Breeding Humans with Anthropoid Apes. *Sci Context* 15(2): 277–316.

220 Lamb D (1988) *Down the Slippery Slope: Arguing in applied ethics*. Routledge, London.

221 *ibid.*

222 *ibid.*

223 Gorovitz S (1983) Progeny, progress and primrose paths. In Gorovitz S, Macklin R, Jameton AL, O'Connor JM and Sherwin S (eds.) *Moral Problems in Medicine*. Prentice Hall, Englewood Cliffs, NJ, p.355–363.

The Council does not think that the creation of embryos specifically for research is currently justified or represents a proportional response while supernumerary IVF embryos exist. This is based on the recognition of the need to avoid the instrumentalisation of embryos and women and on the value of the embryo as a symbol of how we treat each other as members of the human race. This assessment is also cognisant of the current technical limitations of SCNT. Should IVF processes become more efficient, with a resultant decrease in the number of supernumerary embryos available for research, or if the therapeutic potential of SCNT is borne out by research, the balance of the ethical concern over the creation of embryos versus the value to society of such research may have to be re-evaluated. If the creation of embryos for research were deemed to be acceptable at some point in the future, the Council would have no principled objection to the creation of human-animal hybrid cell lines, which would obviate concerns relating to coercion and exploitation of women.

Related Ethical Issues

Umbilical Cord Blood Banking

Currently, there are two modalities of storage of umbilical cord blood. Public, non profit banks collect umbilical cord blood from donors for public use. Access to these banks is universal and many such banks operate as part of international networks in order to ensure the widest possible utilisation of these cells. Commercial banks store umbilical cord blood for the exclusive use of donors or their families, in return for a fee. Recently, Cryo-Cell International, the world's largest commercial umbilical cord blood bank, has patented a method for the collection, processing and freezing of endometrial stem cells found in menstrual blood.[224] Some of the ethical issues pertaining to storage of endometrial stem cells are similar to those posed by banking of umbilical cord blood stem cells.

Anticipating that stem cell research will soon deliver therapies, companies are offering parents the opportunity to store their children's cord blood for their personal use, in the event that they or a member of their family were to develop a disease that could be treated by cord blood stem cell transplantation in the future. The legitimacy of this opportunity has been questioned and there has been considerable debate about whether storing a child's umbilical cord blood is a worthwhile investment for future healthcare, or an expensive procedure that is unlikely to prove beneficial.[225] The probability of needing an autologous (where the donor and recipient are one and the same) transplantation has been estimated as approximately 1 in 20,000 during the first 20 years of life.[226]

224 Cryo-Cell International Inc. (2007) *Cryo-Cell Launches C'elle, First-Ever Proprietary Menstrual Stem Cell Service*. Press release, published 1 November 2007. Available online at: http://www.celle.com/mediaKit _ prSection.aspx, accessed 22 November 2007.

225 European Group on Ethics in Science and New Technologies to the European Commission (2004) *Ethical aspects of umbilical cord blood banking*. Opinion No.19. Brussels.

226 ibid., p.9.

Furthermore, the quantity of cells collected from umbilical cord blood is often not enough for the purposes of transplantation in an adult. Several medical organisations have issued recommendations on the matter and are in agreement that commercial cord blood banks, which charge around €2,000 for collection and storage, are providing a service that has yet to offer any therapeutic options and that this should be made clear in their advertising information.[227,228]

Umbilical cord blood banking for personal use raises ethical issues relating to equitable access to healthcare. If cord blood banking were to be encouraged solely for personal use, as a privately funded commercial enterprise, only the financially privileged would be able to afford the service. In 2002, the French National Advisory Ethics Committee stated that "the principles of justice and equity should predominate" in the decision making process and that if, in the future, storing one's own cord blood cells were to be of value, this personal storage of cord blood should not be left to commercial banks, but be taken in charge by public authorities.[229] Two years later, the EGE echoed this view and advised the European Commission (EC) that if developments showed that an individual's cord blood cells were of medical value to him/herself: "the storage should not be a service left to commercial banks but should be taken over by the public sector in order to ensure fair access to healthcare services for everybody".[230]

However, it is difficult to argue that parents who wish to pay companies to store umbilical cord blood should be prevented from doing so. The majority of members of the EGE considered that: "a strict ban would represent an undue restriction on the freedom of enterprise and the freedom of choice of individuals/couples".[231] Umbilical cord blood storage can be seen as comparable to other forms of medical insurance and parents who can afford to invest in the procedure for personal use should be free to make an autonomous decision. However, appropriate information should be provided to consumers and the practice should adhere to the standards set out in the *European Communities (Quality and Safety of Human Tissues and Cells) Regulations 2006 (Statutory Instrument No.158 of 2006)*.

In response to the success of cord blood transplants in treating blood and immune system diseases,[232,233] rather than based on the promise of future stem cell therapies, public cord blood banks have been established in several countries. In 2004, there were about 100 cord banks worldwide, 75% of which were public or non profit banks. Such public banks were in operation in Austria, Belgium, the Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland,

227 Royal College of Obstetricians and Gynaecologists (2006) *Umbilical Cord Blood Banking*. Scientific Advisory Committee Opinion Paper 2. London.

228 American Academy of Pediatrics Section on Hematology/Oncology, American Academy of Pediatrics Section on Allergy/Immunology, Lubin BH and Shearer WT (2007) Cord Blood Banking for Potential Future Transplantation. *Pediatrics* 119(1): 165–170.

229 French National Advisory Ethics Committee for Health and Life Sciences (2002) *Umbilical cord blood banks for autologous use or for research*. Opinion No.74. Paris.

230 European Group on Ethics in Science and New Technologies to the European Commission (2004) *op. cit.*

231 *ibid.*

232 Broxmeyer HE, Douglas GW, Hangoc G, Cooper S, Bard J, English D, *et al.* (1989) Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *PNAS* 86(10): 3828–3832.

233 Brunstein CG, *et al.* (2007) *op. cit.*

Spain, Switzerland and the UK.[234] Establishing cord blood banks, to which umbilical cord stem cells are donated altruistically and from which all patients can benefit, has been the preferred option in many countries, based on the principle of solidarity, equity of access and on public health considerations.[235]

The Coombe Women's Hospital, the Rotunda Hospital and the National Maternity Hospital at Holles Street have recently agreed not to facilitate the collection and storage of umbilical cord blood for personal use, based on the view that scientific evidence of the value of umbilical cord stem cells is still lacking.[236] However, the hospitals have committed to carrying out the procedure on infants when a recommendation is issued by the Irish Blood Transfusion Service. This would be the case if a newborn's sibling suffers from leukemia, for example.

In the US, cost-benefit analyses evaluating the National Cord Blood Initiative have guided policies of structure and investment in public cord banking.[237] There may be merit in Ireland carrying out its own economic analyses to determine whether a National cord blood bank would be a wise investment for the treatment of blood and immune system disorders, and as a source of potential future stem cell therapies.

If, on the basis of scientific evidence and economic analyses, umbilical cord blood banking were judged to be a useful investment for Irish healthcare, a public rather than private model should be adopted, in order to secure equal access to benefits for all. While the Council remains unconvinced of the utility of commercial cord blood banking for future personal use, a prohibition of the practice would restrict the personal autonomy of individuals who might wish to avail of such a service. Nonetheless, the Council considers that accurate and valid information relating to future therapeutic potential and a statement confirming adherence to the European Union (EU) *Tissue and Cells Directive*, must be provided to prospective clients and that misleading advertising should be prohibited.

234 European Group on Ethics in Science and New Technologies to the European Commission (2004) *op. cit.*

235 Equity of access is enshrined in the European Charter of Patients' Rights, which was recently reviewed in the Irish context in a document commissioned by the Irish Patients Association: O'Mathúna DP, Scott PA, McAuley A, Walsh-Daneshmandi A and Daly B (2005) *Health Care Rights and Responsibilities: A Review of the European Charter of Patients' Rights*. Dublin.

236 The Sunday Independent (2007) Main hospitals veto lifesaving cord-blood bank. *The Sunday Independent,* 23 September 2007. Available online at: http://www.independent.ie/national-news/main-hospitals-veto-lifesaving-cordblood-bank-1085759.html, accessed 6 December 2007.

237 Howard DH, Maiers M, Kollman C, Logan B, Gragert L and Setterholm M (2005) A cost-benefit analysis of increasing cord blood inventory levels. In Committee on Establishing a National Cord Blood Stem Cell Bank Program, Meyer EA, Hanna K and Gebbie K (2005) *On Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program*. The National Academies Press, Washington, DC, p.221–241.

Patenting Stem Cells

During the last decade the patenting of human biological material, so called "patents on life", has engendered significant ethical and legal debate in a number of jurisdictions.[238] Following a divisive legal discussion, extending from North America to Europe, about whether or not it would be appropriate to patent life forms, the patentability of biological material—including genes and cell lines—has been broadly accepted. Thus, uses of human adult stem cells and animal stem cells are generally not controversial in terms of obtaining patent protection. While the granting of patents for adult stem cells is accepted in Europe and elsewhere, based on the condition that informed consent is assigned a central role when obtaining cells, there is a divergence of opinion in relation to the patenting of embryos and stem cells derived from them.

Patents in Europe are granted for inventions that are new, not obvious and industrially applicable. Specific categories of inventions are excluded from patentability. The most relevant of these exclusions in the context of stem cell research can be found in Article 53(a) of the *European Patent Convention*, which states that patents shall not be granted in respect of "Inventions the publication or exploitation of which would be contrary to 'ordre public' or morality".[239] However, no guidance was given on how the morality exclusions of the Convention should be interpreted, until the EU's 1998 *Directive (Directive 98/44/EC) on the legal protection of biotechnological inventions*.[240] Among other provisions, the Directive established, under Article 6, that patents should not be granted (as contrary to morality) in respect of "uses of human embryos for industrial or commercial purposes. The human body, at the various stages of its formation and development…cannot constitute [a] patentable [invention]". The incorporation of the biotechnology Directive into the regulations of the *European Patent Convention* in 1999 (as Rules 23d–e) consolidated ethics as a factor in European patenting decisions and for the first time gave specific guidance on the treatment of patent applications in relation to the human embryo. While the use of human embryos for industrial or commercial purposes was explicitly excluded from patentability under Rule 23d(a), foetal and adult stem cells were considered to fall under the provisions of Rule 23e that allow the patenting of isolated elements of the human body if they constitute more than a mere discovery.

In 1999, the European Patent Office (EPO) issued the University of Edinburgh with a patent for isolating and purifying human embryonic stem cells. The decision met with considerable opposition and a total of 14 groups and individuals registered their objection to the patent on the grounds of "*ordre public*", including the governments of the Netherlands and Italy. In making its decision on the objections to the patent, which was published in July 2003, the EPO considered the morality provisions and concluded that embryonic stem cells were unpatentable in Europe, thereby reversing their original decision to grant the patent. The University of Edinburgh appealed the decision but the appeal was suspended owing to issues arising out of a separate but related patent application to the EPO.

238 For a more detailed discussion on this topic, see the Irish Council for Bioethics (2005) *Human Biological Material: Recommendations for Collection, Use and Storage in Research*. Dublin.

239 European Patent Office (1973–2000) *Convention on the Grant of European Patents (European Patent Convention)*. Available online at: http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/ma1.html, accessed 6 December 2007.

240 *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions*. Official Journal of the European Communities L 213/13 of 30.7.98, Article 6.

In 2004, the EPO rejected a patent application (EP 0 770 125 A1) from Wisconsin Alumni Research Foundation (WARF), relating to primate (including human) embryonic stem cells. The EPO Examining Division rejected the WARF application because the method of manufacture described used a human embryo as starting material for the cell culture and necessitated the destruction of that embryo. In line with the reasoning in the decision on the Edinburgh patent, the embryonic stem cells were not considered to be patentable as this contravened Article 53(a) of the *European Patent Convention* and Rule 23d. The applicants appealed and the technical Board of Appeal at the EPO decided to refer questions for decision to the Enlarged Board of Appeal, the body that rules on points of law.[241] Until a decision has been reached by the Enlarged Board of Appeal on the matter, applications for patents relating to embryonic stem cells have been suspended.[242] It is interesting to note that, unlike the patent system established by the *European Patent Convention*, the patent system in the US does not have express exclusions to patentability within the country's patenting legislation. Nonetheless, a legal challenge to patents held by WARF in the US, relating to human embryonic stem cells and methods for deriving them, was successful, albeit based on technical rather than ethical grounds.[243] In April 2007, the US Patent and Trademark Office, in a preliminary hearing, revoked three embryonic stem cell patents held by WARF based on its judgement that the embryonic stem cells, which had been patented, appeared to be the same as, or clear variations of, cells described in earlier scientific papers or in other patents. In February 2008, this decision was partially reversed when the US Patent and Trademark Office ruled that one of the three patents relating to primate and human embryonic stem cells (Patent no. 913) held by WARF could stand. Decisions on the two other patents are still pending by the patent office.

The European Molecular Biology Organisation (EMBO) has called for the EPO to reconsider its current position, claiming that the EU will suffer as a result of its inability to attract an industrial human embryonic stem cell presence to the territory. The EMBO argues that failure to grant patent protection undermines European competitiveness and future economic and healthcare benefits that might accrue from such research.[244] While it can be argued that patenting stem cells will promote research and development in this field of research by protecting financial investments, and that the requirement of full disclosure in patent applications brings into the public domain information that might otherwise be kept secret, it can equally be argued that patenting has the opposite effect. As previously mentioned, in the US, WARF is the major patent holder in the field of embryonic stem cell research. Geron Corporation, having funded the research, holds exclusive US commercial rights to three cell types derived from embryonic stem cells. Complaints have repeatedly been made that this intellectual property situation is stifling research and investment in the area, as many small biotechnology companies and research laboratories cannot afford the research licences owed to WARF.[245] Several academics and public interest groups were party to the aforementioned challenge to the WARF patents that were recently revoked by the US Patent and Trademark Office.

241 European Patent Office (2006) Decision T 1374/04 of the EPO Technical Board of Appeal of 7 April 2006 *in re* European Patent Application No. 96903521.1 of Wisconsin Alumni Research Foundation. Available online at: http://legal.european-patent-office.org/dg3/pdf/t041374eu1.pdf, accessed 21 December 2007.

242 Not all European countries have adhered to the EPO's moratorium. The UK will grant patents on pluripotent and multipotent embryonic stem cells but not on totipotent stem cells, which have the potential to develop into human beings. Sweden also allows patents on human embryonic stem cells.

243 Check E (2007a) Patenting the obvious? *Nature* 447(7140): 16–17.

244 European Molecular Biology Organisation (2006) *op. cit.* p.69.

245 Wadman M (2005) Licensing fees slow advance of stem cells. *Nature* 435(7040): 272–273.

This illustrates the tensions that can occur between economic interests and cultural values. As the EGE states, it "is necessary to secure the right balance between the inventor's interests and the society's interests, in the sense that one task for the community is to secure ethical principles and values in the context of possible conflicting interests of stakeholders".[246] In the case of non embryonic stem cells, several measures can be taken to ensure that the correct balance is struck: limits can be placed on licensing patented technology to a single entity, thus, avoiding monopolies; the lifespan of patents can be shortened so that the technology becomes widely available earlier; and finally, stricter guidelines for patent claims can be set, such as increasing the patent "utility", to avoid the granting of overly broad patents.

Specific ethical concerns, which have been appealed to in support of the EPO's current policy not to grant patents for modified embryonic stem cells, include concerns that the practise instrumentalises the human embryo to an unacceptable degree. Moreover, opposition to human embryonic stem cell patents in Europe is based on the belief that these patents devalue, infringe or otherwise violate human dignity.[247] In the 2002 EGE *Opinion on the ethical aspects of patenting inventions involving human stem cells*, the Group opined that, patenting unmodified embryonic stem cell lines was like "commercialisation of the human body" and asserted that, strict controls should be enforced so that patents should only be issued on lines that have been modified to create new characteristics for specific industrial applications.[248] The Danish and the French National ethics councils have further stressed that, stem cells, which have not been significantly modified, should not be patentable, based on the principle of non commercialisation of the human body.[249,250] As previously discussed, the concept of human dignity implies the principle of non instrumentalisation and non commodification of human beings and the non commercialisation of the human body and its parts. As the Council considers the human embryo to have significant moral value, and in light of the arguments made in this Opinion relating to commodification of the embryo as a result of its creation specifically for research purposes, it is the view of the Council that patents on embryonic stem cells endanger human dignity, in that they can encourage the treatment of embryos as property.

With a view to balancing progress in the field of stem cell research with equitable and affordable access to any medical products developed, the Council would support adopting measures that limit the breadth and/or duration of non embryonic stem cell patents. The Council also considers that donors should be informed of the patentability of their stem cells and of whether or not they may be commercialised, as part of the informed consent procedure. Given the moral value accorded to human embryos, the Council is opposed to the patenting of embryonic stem cells on the basis of protecting human dignity and avoiding an undue instumentalisation of human life.

246 European Group on Ethics in Science and New Technologies to the European Commission (2002) *Opinion on the ethical aspects of patenting inventions involving human stem cells*. Opinion No.16. Brussels.

247 Caulfield T and Brownsword R (2006) Human dignity: a guide to policy making in the biotechnological era? *Nat Rev Genet* 7(1): 72–76.

248 The European Group on Ethics in Science and New Technologies to the European Commission (2002) *op. cit*.

249 The Danish Council of Ethics (2004) *Patenting Human Genes and Stem Cells. A Report*. Copenhagen.

250 French National Advisory Ethics Committee for Health and Life Sciences (2006) *Commercialisation of human stem cells and other cell lines.* Opinion No.93. Paris.

STEM CELL RESEARCH: LEGISLATION/REGULATION

Stem Cell Research: Legislation/Regulation

A country's choice of policy and law is informed by its value systems, which most often stem from religious and philosophical traditions. Choices may also depend on more recent historical factors and economic imperatives. Several countries worldwide have opted for liberal bioethics legislation concerning research on human embryos and such countries authorise embryonic stem cell research and cloning for research (not reproductive) purposes, though with specific regulations in place. Research in such countries is most usually conditional to ethical approval, carried out under strict regulation and overseen by a National authority. Other countries have adopted a more restrictive position regarding such research and have forbidden embryonic stem cell research and cloning. Somewhere in between, many States are considering or reconsidering their positions on the matter and are currently working with a range of intermediate policies and/or legislation, and with moratoriums or derogations.[251] It is interesting to note that there have been a number of discussions in Europe regarding the legal definition of an embryo and whether this definition encompasses SCNT embryos. For example, in 2002, in response to a previous legal challenge, the UK Court of Appeal ruled that an embryo is an embryo whether it is created by fertilising an egg with sperm or by cloning. (See Appendix E for a detailed view of the various positions that have been adopted globally in relation to the regulation of stem cell research).

Legislation/Regulation of Stem Cell Research in Ireland

While research involving adult stem cells is legal and is being conducted in a number of locations, the regulation of such practices within Ireland has not been without incident. For example, in 2006 a situation arose when it emerged that a doctor in the south of Ireland was treating patients suffering from multiple sclerosis with adult stem cells from umbilical cord blood supplied by a Swiss company.[252,253] As a registered medical practitioner, the doctor was entitled to provide any treatment he considered appropriate and he was not required to have a specific licence to provide stem cell based treatments. However, on 7 April 2006, the EU *Tissue and Cells Directive*[254] came into effect throughout Europe and, consequently, the stem cell treatments being provided were halted pending the granting of the appropriate licence from the Irish Medicines Board.[255] It should be noted that the licence required relates to the procurement (as well as the testing, processing, preservation, storage and distribution) of human tissues and cells, including umbilical cord stem cells.[256]

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251 For a more detailed breakdown of the legislation and regulation of stem cell research internationally, please see Appendix E: Overview of the Legislation on/Regulation of Stem Cell Research Globally.

252 O'Sullivan C (2006) Watchdog probes MS stem cell therapy. *Irish Examiner*, 30 March 2006.

253 The Irish Times (2006) IMB investigates stem cell treatment in Cork. *The Irish Times*, 30 March 2006.

254 The *EU Tissue and Cells Directive* refers to *Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.*

255 *Directive 2004/23/EC* and the *Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells*, were transposed into Irish law on 7 April 2006 under the *European Communities (Quality and Safety of Human Tissues and Cells) Regulations 2006* (Statutory Instrument No. 158 of 2006).

256 Irish Medicines Board (2007) *Guidance on the regulatory requirements for the procurement, in the Republic of Ireland, of human tissues and cells intended for human application*. Dublin, p8.

Notwithstanding the situation regarding adult stem cell research, Ireland currently has no specific legislation dealing with embryonic stem cell research and, furthermore, it does not have a legislative basis for the practice of IVF.[257] Therefore, Ireland has no legislation pertaining to the use of embryos for research, whether these embryos were produced for infertility treatment or specifically for research purposes.

Following a referendum in 1983, the *Constitution of Ireland* (1937) was amended and Article 40.3.3 of the Constitution now provides: "The State acknowledges the right to life of the unborn and, with due regard to the equal right to life of the mother, guarantees in its laws to respect, and, as far as practicable, by its laws to defend and vindicate that right." However, no legislation followed this amendment, *e.g.* to articulate what is defined as the "unborn" and it is unclear whether this constitutional framework provides protection to the preimplantation embryo, that is, supernumerary IVF embryos. Article 40.3.3 has been interpreted by some to mean that embryonic stem cell research would be prohibited under the Constitution. A recent High Court judgement (November 2006) found that three frozen embryos resulting from IVF were not "unborn" as defined under the Constitution.[258] In his judgment of the case, Mr. Justice McGovern stated that:

> There has been no evidence adduced to establish that it was ever in the mind of the people voting on the Eight [*sic*] Amendment to the Constitution that "unborn" meant anything other than a foetus or child within the womb. To infer that it was in the mind of the people that "unborn" included embryos outside the womb or embryos in vitro would be to completely ignore the circumstances in which the amendment giving rise to Article 40.3.3 arose. While I accept that Article 40.3.3 is not to be taken in isolation from its historical background and should be considered as but one provision of the whole Constitution, this does not mean that the word "unborn" can be given a meaning which was not contemplated by the people at the time of the passing of the Eight Amendment and which takes it outside the scope and purpose of the amendment.[259]

The High Court judgment has been appealed to the Supreme Court and at the time of writing the case has not yet been heard.

The sixth edition of the Medical Council's *A Guide to Ethical Conduct and Behaviour* states, in relation to IVF, that "any fertilised ovum must be used for normal implantation and must not be deliberately destroyed".[260] The guide also states that, "the creation of new life forms for experimental purposes or the deliberate and intentional destruction of in-vitro human life already formed is professional misconduct". However, the Medical Council, through its ethics committee, is in the process of reviewing this edition of its guide. It should be noted that the Medical Council only regulates physicians and scientists are not bound by the guide, therefore, it would appear that there is currently no legal impediment on the importation or use of embryonic stem cell lines by scientists.

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257 European Group on Ethics in Science and New Technologies to the European Commission (2007) *Recommendation on the ethical review of hESC FP7 research projects*. Opinion No.22. Brussels.

258 *M.R. v T.R. & Ors* [2006] I.E.H.C. 359.

259 *ibid.*

260 Medical Council (2004) A *Guide to Ethical Conduct and Behaviour.* Sixth Edition. Dublin.

In 2000, the then Minister for Health, Mr. Micheál Martin, T.D., established the CAHR to provide recommendations to the Irish Government in regard to all aspects of AHR, including IVF practices, gamete donation and surrogacy. In addition, the CAHR made recommendations relating to the use of embryos in stem cell research, as well as research and reproductive cloning.[261] The CAHR members, with one exception, recommended that, "embryo research, including embryonic stem cell research, for specific purposes only and under stringently controlled conditions, should be permitted on surplus embryos that are donated specifically for research".[262] The CAHR advised that the creation of IVF embryos specifically for research should be prohibited but all CAHR members, with one exception, recommended that the creation of SCNT embryos for research should be allowed. The CAHR further recommended that, both reproductive cloning and the generation and use of interspecies or hybrid embryos should be prohibited.

The CAHR was of the view that a regulatory body should be established to control AHR in Ireland, including clarifying under what conditions and for what purposes embryo research would be permitted. Nonetheless, it should be noted that it is a matter for the Oireachtas[263] as to whether it implements the recommendations of the CAHR. Until such a time as a definitive decision is made by the Government directly, by a public referendum or through the Supreme Court, the legality of research involving embryos in Ireland will remain unclear.

European Regulatory Framework

Notwithstanding the lack of specific legislation pertaining to stem cell research in Ireland, within Europe there are a number of overarching regulatory frameworks in existence, which have implications for the legislative and regulatory processes for stem cell research that are adopted in Ireland.

The *European Convention on Human Rights and Biomedicine* (1997) makes a number of references to research involving embryos and cloning.[264] Article 18.1 of the Convention permits research on embryos *in vitro* where the National legislation allows, provided the embryos are afforded sufficient protection. Article 18.2 expressly forbids the creation of human embryos for research purposes.

As of March 2008, 34 Member States of the Council of Europe have signed the Convention, and 21 of these have ratified it.[265] The Convention is only binding in Member States that have ratified it, a situation that has implications for the regulation of research involving embryos in countries such as France, Germany, the Netherlands and Sweden, which have signed but not yet ratified the Convention. In addition, it should be noted that neither Ireland nor the UK have signed the Convention. In 2002, the then Minister for State at the Department of Health and Children, Mr. Ivor Callely, T.D., stated in

261 The Commission on Assisted Human Reproduction (2005) *op. cit*. p.151.

262 *ibid.*

263 The Oireachtas is the National Parliament of Ireland.

264 Council of Europe (1997) *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. Oviedo, 4.IV.1997. Available online at: http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm, accessed 7 August 2007.

265 Status as of 19 March 2008. See http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=7&DF=3/19/2008&CL=ENG, accessed 19 March 2008.

a Seanad Éireann[266] debate: "Ireland is not a signatory to the Convention because there are difficulties with a number of articles that have implications for the destruction of human embryos".[267]

Another pan-European initiative saw the formation of the Group of Advisers on the Ethical Implications of Biotechnology (GAEIB) to the EC in 1991. The GAEIB was established to examine the ethical questions associated with biotechnology. In May 1997, the GAEIB produced an opinion document entitled *Ethical Aspects of Cloning Techniques*, which made a number of recommendations concerning cloning research involving humans and animals. This document recommended that human reproductive cloning should be prohibited and that any research involving nuclear substitution (SCNT) in human embryos should be conducted to help overcome disease and alleviate suffering.[268]

In 1997, the GAEIB was replaced by the EGE. Since then, the EGE has produced a number of opinion documents that are relevant to the field of stem cell research and in which the Group supported using embryonic stem cells for research under certain circumstances. In November 1998, the EGE published the document *Ethical aspects of research involving the use of human embryos in the context of the 5th framework programme*, which stated that the human embryo deserved legal protection and that such protection falls under the remit of National legislation. In addition, this document recognised the difficulty in standardising such legislation throughout individual Member States and thus acknowledged that it would be inappropriate for the EU to impose "one exclusive moral code". Furthermore, the document recommended that any research on human embryos, whether in the public or the private sector, should be under strict public control and conducted with maximum transparency.[269]

The EGE published the opinion *Ethical aspects of human stem cell research and use* in November 2000.[270] In this document, the EGE again acknowledged the right of individual Member States to legalise and appropriately regulate embryo research; the Group believes that such regulation should be overseen by a centralised authority. The document also states that the creation of embryos, using gametes, for stem cell research is ethically unacceptable. In addition, the EGE favoured a precautionary approach to the creation of embryos for stem cell research using SCNT and it suggested that alternative sources of stem cells, *e.g.* adult stem cells, foetal tissues or supernumerary IVF embryos, should be examined first.

266 The Seanad is the Upper House of the Irish Parliament.

267 See Seanad Éireann debates, Volume 170, 4 December 2002. Available online at: http://historical-debates.oireachtas.ie/S/0170/S.0170.200212040008.html, accessed 6 December 2007.

268 Group of Advisers on the Ethical Implications of Biotechnology to the European Commission (1997) *Ethical aspects of cloning techniques*. Opinion No.9. Brussels, p.7.

269 European Group on Ethics in Science and New Technologies to the European Commission (1998) *Ethical aspects of research involving the use of human embryo in the context of the 5th framework programme*. Opinion No.12. Brussels, p.12.

270 European Group on Ethics in Science and New Technologies to the European Commission (2000) *Ethical aspects of human stem cell research and use*. Opinion No.15. Brussels, p.20.

European Funding of Stem Cell Research

Wide ranging discussions relating to the acceptability of embryonic stem cell research in Ireland were, in large part, prompted by the European funding of such research under EU Framework Programmes six and seven. The Framework Programme (FP) is the EU's main instrument for funding research and development.

Under FP6 (2002–2006) it was required that all research activities would respect fundamental ethical principles, including those outlined in the *Charter of Fundamental Rights of the European Union* (2000). It was also well recognised that, throughout Europe, there were diverse views regarding research involving embryos and embryonic stem cells, however, in agreement with the principle of subsidiarity (decisions which are taken by individual Member States), anyone participating in research under FP6 had to comply with the relevant legislation, regulations and ethical rules in the countries where the research was to be conducted. Furthermore, it was not possible under FP6 for the EU to fund in a Member State any research that was prohibited in that State.[271] It was decided that FP6 could be used to fund research using human embryos and human embryonic stem cells except in three particular areas, namely:

- Research activity aimed at human cloning for reproductive purposes (reproductive cloning).
- Research activity intended to modify the genetic heritage of human beings, which could make such changes heritable.
- Research activities intended to create human embryos solely for the purpose of research or as a source of stem cells, including through the use of SCNT.
- Research activities, which destroy human embryos, including for the procurement of stem cells.[272]

In addition, all research projects were required to seek the relevant ethical approval before they could begin. To aid in this process, the EC was tasked with conducting an ethical review for research involving human embryos and human embryonic stem cells.

Following the adoption of FP6, the EC implemented a moratorium on funding and since then no funding has been allocated for research on human embryonic stem cells, apart from projects that involved already stored or isolated human embryonic stem cells.[273] In July 2003, an attempt was made to modify the eligibility for funding under FP6 to include research involving stem cells obtained from supernumerary IVF embryos.[274] While the European Parliament was in favour of this proposal, it did

271 The Council of the European Union (2002/834/EC) *Council Decision of 30 September 2002 adopting a specific programme for research, technological development and demonstration: 'Integrating and strengthening the European Research Area' (2002–2006).* Official Journal of the European Communities L294/1 29.10.2002. "In any case, national provisions apply and no research forbidden in any given Member State will be supported by Community funding in that Member State". Available online at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002D0834:EN:HTML, accessed 6 December 2007.

272 The Council of the European Union (2002/834/EC) *op. cit.*, Research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer shall not be financed.

273 European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*.

274 Commission of the European Communities (2003) *Proposal for a Council decision amending decision 2002/834/EC on the specific programme for research, technological development and demonstration: "Integrating and strengthening the European research area" (2002–2006).* Brussels, 9.7.2003, COM (2003) 390 final, 2003/0151 (CNS).

not receive a qualified majority at the subsequent meeting of the Council of Europe in December 2003.[275] Although this proposal would have enabled new sources of embryonic stem cells to be used for research, the proposal also included stricter guidelines and safeguards for embryonic stem cell research. The Irish Government voted in favour of this proposal; the rationale provided was that it did not wish to see unregulated stem cell research being conducted elsewhere in the EU.[276,277,278] On 31 December 2003, the moratorium on funding ended and the implementation of research projects was allowed under FP6.

Therefore, under FP6 and now also with FP7 (2007–2013) funding of research involving embryos and embryonic stem cells is permitted—provided the relevant ethical and legal conditions are met in the country where the research will take place. However, a diverse range of regulatory frameworks exist throughout Europe with regard to such research, which reflects the cultural diversity and autonomy of the individual EU Member States.

In the case of Ireland, due to the uncertainty around the legal status of embryonic stem cell research here, public funding is restricted to adult stem cell research. The Irish Government's position on European funding for embryonic stem cell research is that no EU funding for embryonic stem cell research will be permitted in Ireland. Nevertheless, Ireland does respect the decision of other Member States to participate in such research. This position was reinforced in 2006 by the Minister for Enterprise Trade and Employment, Mr. Micheál Martin, T.D., who saw the decision to continue to provide funding for embryonic stem cell research in those countries where it was permitted, as a vote in favour of "ethical subsidiarity".[279] Nonetheless, within Ireland, concerns have been raised regarding the ethical consistency of this subsidiarity argument, since it allows EU funds, a proportion of which were provided by Irish taxpayers *via* the Irish Government, to be used to conduct in other jurisdictions embryonic stem cell research that is not permitted in Ireland.

It is the view of the Council that, a failure to provide a comprehensive and cohesive regulatory system to govern stem cell research and its applications undermines the moral value of the human embryo. It may also hinder developments in this field of research in Ireland. Thus, the Council recommends the establishment of a State funded regulatory authority, which would function independently and transparently (in its principles and agenda), to oversee embryo research. Such an authority should be tasked with the registration, licensing and inspection of persons/premises/activities working with human embryos and/or embryonic material. Furthermore, the authority should develop codes of good practice for professionals working in the area and provide accessible information for the public.

275 European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit.*

276 See Seanad Éireann debates, Volume 174, 19 November 2003. Available online at: http://historical-debates.oireachtas.ie/S/0174/S.0174.200311190008.html, accessed 6 December 2007.

277 Beesley A (2003) Taoiseach disputed cardinal's stance on stem cells. *The Irish Times*, 24 December 2003.

278 Staunton D (2003) No decision reached on funding stem cell research. *The Irish Times*, 4 December 2003.

279 Smyth J (2006) EU to provide stem-cell research funding. *The Irish Times*, 25 July 2006.

APPENDICES

Appendix A: The Results of the Public Consultation

Introduction

As in the case of previous studies undertaken by the Irish Council for Bioethics, a public consultation on the issue of stem cell research was carried out in line with its established policy. From its institution, the Council has considered it essential that, as the topics it investigated would—to a greater or lesser extent—concern the general public, the population at large should be canvassed for its opinions and comments. In each consultation, to date (including the present one), the approach was to make available a detailed questionnaire covering all the salient points of the topic under review, following its notification by advertisements and general publicity in the media (See Appendix B).

While the questionnaires issued have been carefully designed, there is always the possibility that some aspect of public interest may not have been covered by the specific questions and, with this in mind, each questionnaire has incorporated an "open" section, in which respondents are given the opportunity to express their opinions at will (and at their chosen length) and to raise any further matters they may regard as significant. It has uniformly been the case with the questionnaires issued to date that many respondents have availed of the opportunity provided by the open section to express themselves as they desired. In doing so, they have provided the Council with a considerable body of valuable information to supplement that elicited by the specific questions posed.

In the present study, the questionnaire posed some questions that had "open" possibilities and respondents were given the opportunity to comment briefly under the specific question heading in addition to having available the general open section just discussed. The questionnaire was available online and in hard copy and is presented below in Insert 1.

As a considerable number of submissions referred to various aspects of the questionnaire and its design, this topic is discussed in detail below.

Information Leaflet

The topic of stem cell research is highly complex and the Council was concerned that prospective respondents to the consultation might not have available to them sufficient detailed information regarding the scientific aspects of the subject, to permit them to arrive at a considered opinion on the matter. The Council accordingly prepared an information leaflet, in which the technical aspects of adult and embryonic stem cells, and the procedure of cloning, were explained in a straightforward manner. This leaflet is presented below in Insert 2.

The Aims of the Consultation

As an initial comment, it should be stated that, the exercise described in this Appendix was a consultation and not a survey. As the former, it was intended to solicit, by the means considered most practicable (notification to the public *via* the media, the use of a questionnaire and the preparation and issuing of an explanatory leaflet), the views of members of the public on the project being undertaken by the Council. The nature and degree of response, therefore, would depend on the awareness of the public of the exercise and their interest in it.

The Council was of the view that public awareness of the details and complexities of stem cell research, in any form, was likely to be quite low, partly because of the limited exposure of the subject to date in the media and partly because of confusion engendered by the indiscriminate use of the term "stem cell research", without any qualifying indication as to the nature or source of the stem cells being referred to. Hence, an aim of the consultation was to ascertain the views of the respondents as to the availability or otherwise of accurate, unbiased information on the topic. A second—more important—aim was to facilitate debate on stem cell research in all its forms and, most significantly, to obtain from respondents' comments and opinions a valuable input to the deliberations of the Council on the topic. It was never the intention that the consultation should obviate any perceived need for an exhaustive National debate on stem cell research.

It may be added that a survey would have required wholly different (and quantitative) techniques, as well as a different philosophical approach. Further, the probability of a survey providing the required data was likely to be low because of the presumed low level of awareness of the public about stem cell research.

The Purpose of this Appendix

Rather than interrupt the main flow of the Opinion proper, it was decided (as with previous projects) to place the details of the consultation process, including the findings, in an Appendix. It is important that the reader should be aware that the sole aim of the Appendix is to present the consultation data in a collated form that can be conveniently scrutinised.

Accordingly, there is no discussion whatever on these pages of the many issues raised; such analysis belongs to the Opinion. The total number of submissions in the consultation is 2,188. A total of 1,124 respondents presented observations in the general open section following the series of questions.

Insert 1: Questionnaire

Public Consultation on Stem Cell Research

The Irish Council for Bioethics is considering the ethical issues surrounding adult and embryonic stem cell research and wishes to survey public opinion in Ireland on this matter. Please use this form to let us know your views. Responses will be treated as confidential. Extracts of unattributed comments made in section 14 may be quoted in the final report. Thank you for taking the time to respond.

Questionnaires must be returned to the Irish Council for Bioethics, Regus House, Block 4, Harcourt Centre, Harcourt Road, Dublin 2, by Monday 30th April 2007.

Gender

☐ Male

☐ Female

Residence

☐ Ireland

☐ Other

Age Group

☐ 16–25

☐ 26–35

☐ 36–45

☐ 46–55

☐ 56–65

☐ 66+

Education

☐ Primary

☐ Lwr Secondary*

☐ Upr Secondary†

☐ Third Level

Religious Beliefs

☐ Yes

☐ No

*Lower Secondary equivalent to Junior Certificate †Upper Secondary equivalent to Leaving Certificate

Q1 **How much do you know about stem cell research?**

☐ **a.** I know a great deal about it

☐ **b.** I know a fair amount about it

☐ **c.** I know just a little about it

☐ **d.** I have heard of but know nothing about it

☐ **e.** I have never heard of it

Answers a-d, proceed to Q2. Answer e, skip to Q4.

Q2 **Where do you get information on stem cell research?** (several boxes may be ticked)

☐ Newspapers ☐ Television

☐ Radio ☐ Magazines

☐ The Internet ☐ Friends/Family/Colleagues

☐ Other _____

Q3 Have you heard of the following sources of stem cells?

Adult human tissue,e.g., hair, skin, bone marrow.	☐ Yes	☐ No
Umbilical cord blood collected immediately after birth	☐ Yes	☐ No
Amniotic fluid, i.e., protective fluid surrounding the developing foetus	☐ Yes	☐ No
Foetal tissue obtained from aborted/miscarried foetuses	☐ Yes	☐ No
Human embryos produced but not used, during in vitro fertilisation (IVF) treatment	☐ Yes	☐ No
Human embryos produced specifically for research	☐ Yes	☐ No

Q4 At what point do you believe an embryo acquires full moral status?

- ☐ Fertilisation (i.e., when the sperm and egg join to form an embryo)
- ☐ When the embryo implants itself in the womb
- ☐ At a later time during the pregnancy
- ☐ At birth
- ☐ Other _____
- ☐ Don't know

Q5 Do you think it is acceptable to use embryos produced, but not used, during IVF treatment for stem cell research in Ireland? Using these embryos would lead to their destruction.

☐ Yes ☐ No ☐ Don't know

Q6 Do you think it is acceptable to import embryonic stem cell lines into Ireland for stem cell research?

☐ Yes ☐ No ☐ Don't know

Q7 Do you think it is acceptable to produce cloned embryos as a source of embryonic stem cells?

☐ Yes ☐ No ☐ Don't know

Q8 Do you think it is acceptable to produce cloned human-animal hybrid embryos as a source of embryonic stem cells?

☐ Yes ☐ No ☐ Don't know

Q9 Would you be willing to use medical treatments that were developed using embryonic stem cells?

☐ Yes ☐ No ☐ Don't know

Q10 To what extent do you agree/disagree with the following statements?

(A) Using adult stem cells does not involve the destruction of embryos, therefore scientists should only conduct adult stem cell research.

☐ Strongly agree ☐ Stongly disagree ☐ Don't Know
☐ Moderately agree ☐ Moderately disagree

(B) Scientists should conduct both adult and embryonic stem cell research as we do not currently know which offers more potential for developing medical treatments.

☐ Strongly agree ☐ Stongly disagree ☐ Don't Know
☐ Moderately agree ☐ Moderately disagree

(C) As long as the parents of the embryo give their permission and the embryo would otherwise be allowed to perish, embryonic stem cell research should be permitted on embryos that have not been used for IVF.

☐ Strongly agree ☐ Stongly disagree ☐ Don't Know
☐ Moderately agree ☐ Moderately disagree

(D) If scientists believe that embryonic stem cell research will increase our ability to prevent or treat serious diseases, we should trust them and let them do it.

☐ Strongly agree ☐ Stongly disagree ☐ Don't Know
☐ Moderately agree ☐ Moderately disagree

(E) Using cells from human embryos for medical research comes too close to allowing scientists to play God.

☐ Strongly agree ☐ Stongly disagree ☐ Don't Know
☐ Moderately agree ☐ Moderately disagree

(F) Allowing any research using stem cells from human embryos should be forbidden because it is unethical and immoral.

☐ Strongly agree ☐ Stongly disagree ☐ Don't Know
☐ Moderately agree ☐ Moderately disagree

Q11 Do you think there is a need for specific legislation concerning stem cell research in Ireland?

☐ Yes ☐ No ☐ Don't know

Q12 If embryonic stem cell research were permitted in Ireland, who do you think should be responsible for funding it? (Several boxes may be ticked).

☐ Government

☐ Industry (e.g. pharmaceutical)

☐ Public/Private partnerships

☐ Other _____

☐ Don't know

Q13 In relation to stem cell research, what issues would you like to know more about? (Several boxes may be ticked).

☐ What is the current status of the development of medical treatments using stem cell research?

☐ What are the differences between adult and embryonic stem cells?

☐ What are the potential benefits and risks of adult and embryonic stem cell research?

☐ What ethical considerations are raised by stem cell research?

☐ What stem cell research is taking place in Ireland?

☐ Other _____

☐ Don't know

Q14 Please use this space to express any additional views you may have on stem cell research. (Additional pages can be used).

_____

_____

_____

_____

_____

_____

_____

Please return forms to: Public Consultation/ Stem Cells, Irish Council for Bioethics, Regus House, Block 4, Harcourt Centre,Harcourt Road, Dublin 2, by Monday 30th April 2007.

Insert 2: Information Leaflet

Adapted from the US National Institute of Health Stem Cell Basics, the Medical Research Council UK Stem Cells, and the International Society for Stem Cell Research Frequently Asked Questions on Stem Cell Research.

Q1 What is a stem cell?

Stem cells are immature cells that have the potential to develop into any one of the 216 different cell types that make up the human body, such as heart, liver and skin cells. Stem cells serve as a sort of repair kit for the body; they can divide an unlimited amount of times and replenish dead and damaged cells. Scientists are just beginning to understand what causes stem cells to divide almost indefinitely and what causes them to specialise into other types of cells.

Q2 Why are stem cells important?

Scientists are trying to find ways to grow stem cells in the laboratory and make them generate specific cell types so they can be used to treat injury or disease. Some examples of potential stem cell therapies include replacing the dopamine-producing cells in the brains of Parkinson's patients, developing insulin-producing cells for type I diabetes, and repairing damaged heart muscle following a heart attack with cardiac muscle cells.

Gaining information on the behaviour of stem cells will also shed light on the processes at work during early human development. This knowledge could be important in understanding, and possibly preventing, birth defects. It may also be possible for stem cells to be used as a source of healthy human cells for testing the effectiveness and possible side effects of new drugs.

Q3 Where do stem cells come from?

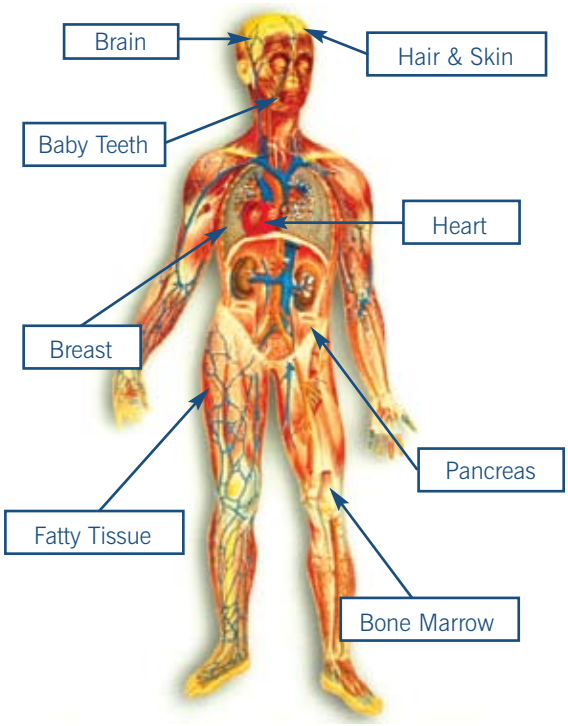
Stem cells are found throughout the body and are present from just after the fertilisation of an egg right through to adulthood. Scientists primarily work with two kinds of stem cells from animals and humans: adult stem cells and embryonic stem cells.

What are Adult Stem Cells?

The term adult stem cell is slightly misleading since these stem cells are found in babies, children and adults, and even in umbilical cord blood. Recently, scientists have discovered stem cells in amniotic fluid, the fluid that surrounds the unborn baby, and these cells may also have the potential to form multiple cell types. Adult stem cells can be obtained from many parts of the body, including bone marrow, brain, blood, skin, eye, muscle, liver and hair. Their job is to replace and replenish cells that are continually being lost due to disease and everyday wear and tear.

Adult stem cells are somewhat restricted in the number of cell types they can develop into. Typically, they can generate the cell types of the tissue in which they are found, for example, blood-forming adult stem cells in the bone marrow are able to generate the three different types of cell that make up the blood. However, recent research suggests that given the right conditions, adult stem cells may be more flexible than was previously thought, a phenomenon known as plasticity. Exploring the possibility of using adult stem cells for therapies has become a very active area of research.

Sources of Adult Stem Cells



(Scott Camazine/ Science Photo Library)

What are Embryonic Stem Cells?

When a sperm cell fertilises a human egg, a one-cell embryo is formed. This embryo then divides three times to make a ball of eight stem cells. These cells, which are known as totipotent embryonic stem cells, have the potential to develop into the 216 different cell types that make up the human body, as well as those that form the placenta and umbilical cord. If the group of cells splits apart at this stage, identical twins or triplets etc. begin to develop. After four or five days of dividing, the embryo consists of a hollow ball of 50 to 100 cells called a blastocyst. The outer layer of the blastocyst forms the placenta and the inner part is made up of embryonic stem cells. At this stage, the embryonic stem cells are said to be pluripotent, meaning they are able to develop into almost all the different types of cells needed to form the human body. They cannot, however, form the placenta and umbilical cord. Scientists can remove these embryonic stem cells from the 5 day-old embryo and grow them in the laboratory. This procedure results in the destruction of the embryo.

There are two main sources of human embryonic stem cells for research. The majority are obtained from embryos produced, but not used, during in vitro fertilisation (IVF) treatment. For many reasons, including the completion of a family or separation from a partner, the embryos made for IVF may not all be used by the couple undergoing treatment. Currently, there are four options for embryos that are not used during IVF treatment: they can be placed in storage, allowed to perish, donated to someone else for IVF treatment, or donated for use in stem cell research. Alternatively, embryonic stem cells can be obtained from embryos made by somatic cell nuclear transfer (SCNT), a technique otherwise known as cloning (see Q6 below). Foetal stem cells, which have similar properties to embryonic stem cells, are also used for stem cell research and are obtained from aborted or miscarried foetuses.

Stem Cell Cultivation

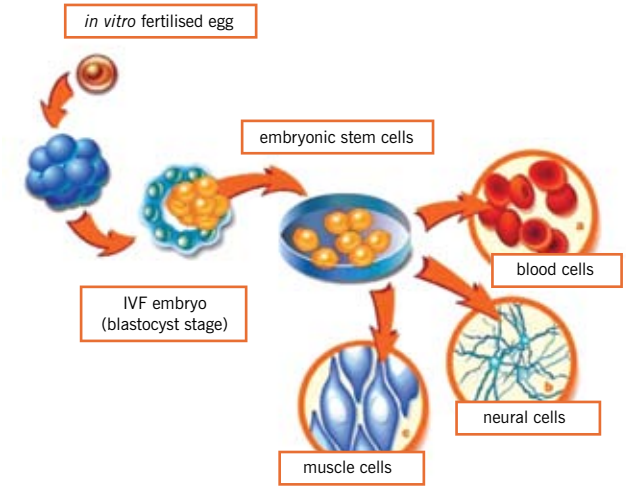


Illustration adapted from the University of Wisconsin

Characteristics of Embryonic and Adult stem cells.

Embryonic Stem Cells	Adult Stem Cells
They are relatively plentiful and are relatively easily grown in the laboratory.	They are present in small numbers and are difficult to access. They can also be difficult to grow in the laboratory.
They can develop into any types of cell found in the body.	Currently, they are known to develop into a restricted number of different cell types, usually related to the type of tissue they are found in.
They would not be genetically identical to the individual being treated and could possibly be rejected by his/her immune system.	They would be genetically identical to the individual being treated and may not be rejected by his/her immune system.
If not fully differentiated into a cell with a specialised function, embryonic stem cells can form tumours.	There is no evidence to suggest that cells and tissues derived from adult stem cells will develop tumours.

Q4 What are stem cell lines?

A stem cell line is a batch of cells that can be grown for long periods of time in the laboratory. These cell lines are grown in incubators under conditions resembling those found in the human body and are commonly used for research experiments. Embryonic stem cell lines, in particular, can be grown indefinitely if the correct conditions are met. Importantly, these stem cell lines retain their ability to form different cell types.

Q5 What are the differences between adult and embryonic stem cells?

Embryonic and adult stem cells each have advantages and disadvantages. First of all, they differ in the amount and type of different cells they can become: embryonic stem cells are either totipotent or pluripotent and can give rise to all of the cell types of the body, whereas adult stem cells are multipotent, meaning they are generally limited to specialising into the different cell types of their tissue of origin.

Large numbers of cells will be needed for stem cell replacement therapies. Embryonic stem cells can be relatively easily grown in culture, while adult stem cells are rare in mature tissues, and methods for expanding their numbers in the laboratory have not yet been perfected.

A potential advantage of using adult stem cells is that the patient's own cells could be multiplied in the laboratory and then reintroduced into his/her body. The use of a patient's own stem cells could mean that they would not be rejected by the immune system. This would represent a significant advantage as immune rejection is a difficult problem that can only be overcome with immunosuppressive drugs. Embryonic stem cells from a donor may cause transplant rejection, however, this has not yet been determined in human experiments.

As embryonic stem cells grow very fast, scientists must be very careful in fully differentiating them into specialised cells for treatment, because any remaining stem cells could grow out of control and form tumours. Adult stem cells, on the other hand,may contain more genetic abnormalities than embryonic cells due to exposure to sunlight and toxins.

Currently, it is very difficult to predict which type of stem cell, adult or embryonic, might be most successful in treating various diseases and conditions. Most scientists believe that for optimal results research should be done on both types of stem cells.

Q6 What is cloning?

Cloning, also known as somatic cell nuclear transfer (SCNT), is a technique in which the nucleus (where the genetic material is carried) of a somatic cell (any cell of the body except for sperm and egg cells) is injected, or transplanted, into an egg that has had its nucleus removed. The resulting embryo is a near identical match to the individual or animal that the original somatic cell was taken from. SCNT has been used by scientists to clone animals for a number of years, the most famous example being Dolly the sheep.

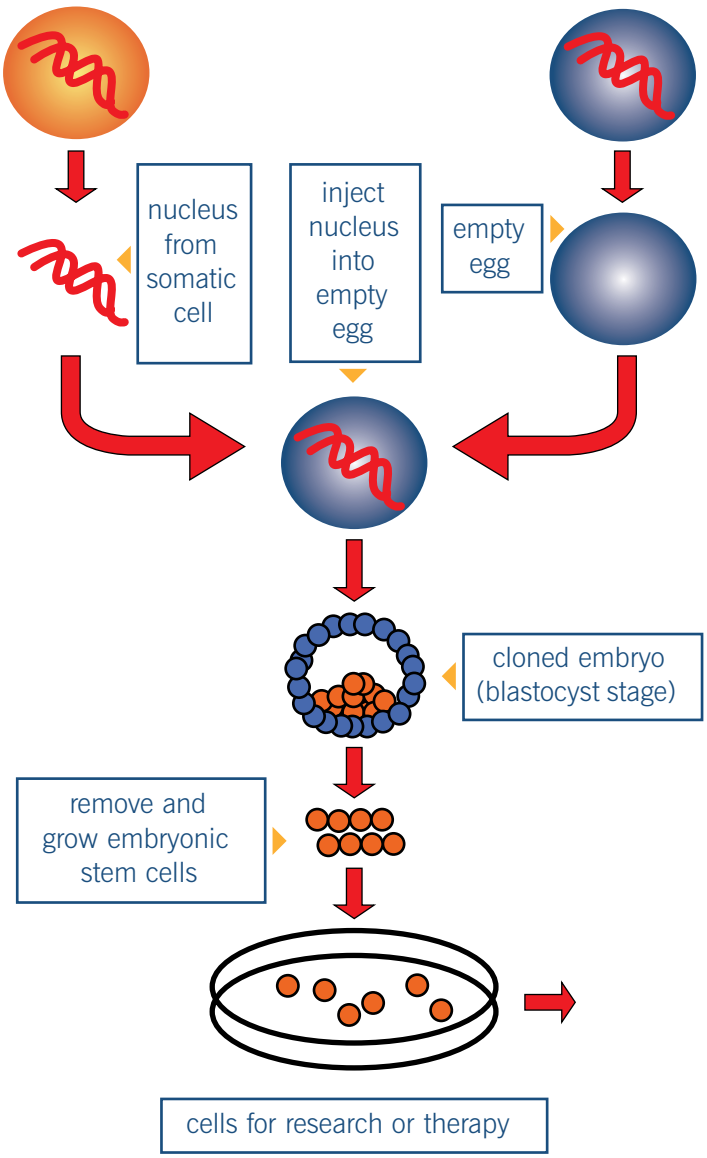
Recently, scientists have used cloning to fuse human somatic cells with animal eggs. The resulting embryos are known as human-animal hybrids. Cloning requires a large supply of human eggs, and their production and isolation involves physical risks for the women donors. It is hoped that by creating hybrid embryos, scientists could avoid using eggs from women to produce embryos for stem cell research.

What is the difference between therapeutic cloning and reproductive cloning?

In reproductive and therapeutic cloning, a cloned embryo is produced by SCNT. The two processes only differ in their use of this cloned embryo. In reproductive cloning, the embryo created by SCNT is implanted into a womb in the hope of producing a viable foetus and bringing it to term. The clone would be a near identical genetic copy of the adult whose somatic cell nucleus was used for cloning. Reproductive cloning has only been used in animals and the process is very inefficient (only about 1 percent develop into normal surviving clones). In addition, the clones that survive often present severe health problems. Generally speaking, governments and scientists are opposed to the reproductive cloning of human beings.

Therapeutic cloning is the process by which a human embryo is created by SCNT in order to obtain embryonic stem cells for research purposes. If the somatic cell is supplied by a patient, the embryonic stem cells isolated from the cloned embryo could be used to make cells and tissue that would not be likely to be rejected by the patient's immune system because they have the same genetic material. In this way, therapeutic cloning could allow 'customised' embryonic stem cells to be generated.

Therapeutic Cloning



Q7 Can embryonic stem cells be obtained without destroying an embryo?

Scientists are working on alternative methods for obtaining embryonic stem cells. However, these methods will require supplementary research using embryos to be developed.

One approach which is being examined is a variation of SCNT: altered nuclear transfer. A gene necessary for the implantation of the embryo into the womb is removed from the donor nucleus before it is inserted into the egg. Therefore, the embryo that develops cannot implant, but embryonic stem cells can be obtained from it. Another approach involves reprogramming adult stem cells to revert back to an embryonic state, a process known as dedifferentiation.

Scientists have also suggested removing one totipotent stem cell from the early 8-cell embryo and generating embryonic stem cells from that cell. However, there is concern that the process will cause unnecessary damage to the remaining embryo.

Q8 Have stem cells been used successfully to treat any diseases?

Scientists first became aware of the existence of adult stem cells in the 1960s. For the last 30–40 years, adult stem cells have been used in bone marrow transplants to treat leukaemia and other types of cancer, as well as various blood disorders. Adult stem cells are also being used to repair damaged skin and corneas (the front cover of the eye). Current research is looking at the ability of adult stem cells to treat diseases such as heart disease, diabetes and advanced kidney cancer. Human embryonic stem cells were first isolated in the laboratory in 1998 and researchers are hoping they will lead to treatments for a number of diseases and injuries, such as Parkinson's disease, Alzheimer's disease, spinal cord injury, stroke, and type I diabetes.

There are many ways in which human stem cells can be used in basic and clinical research. However, there are many technical hurdles remaining between the promise of stem cells and the realisation of these uses.

Q9 Is stem cell research legal in Ireland?

Research on adult stem cells is legal and is currently being conducted in a number of locations in Ireland. In some cases, this research has been publicly funded. The legal situation regarding embryonic stem cell research is less well defined and only research using embryonic stem cells from animals is carried out in Ireland. Ireland does not have specific legislation dealing with stem cell research or research on embryos produced, but not used, during IVF treatment. The Medical Council, which regulates doctors, produced guidelines in 2004 that forbid the deliberate destruction of embryos as well as the creation of embryos specifically for use in research. However, these guidelines do not apply to scientists. Article 40.3.3 of the Constitution of Ireland acknowledges the right to life of the unborn. However, a recent High Court judgement (November 2006) found that three frozen embryos produced during IVF treatment were not considered "unborn" as defined under the Constitution. Therefore, it would appear that embryonic stem cell research and the importation of embryonic stem cell lines created in other countries is not illegal in Ireland. The High Court judgement has been appealed to the Supreme Court, where the matter may be further clarified.

Note on the Questionnaire Responses

It is important to note that each of the responses was examined carefully, so that the views of the respective respondents were ascertained and recorded accurately. It will be apparent, therefore, that with over 1,000 individual comments submitted, a considerable effort was required in their processing. The approach taken was to ensure that the clearly intended views of respondents, on whatever aspects of stem cell research and its implications they referred to, were recorded accurately under one or more headings, as appropriate. No relevant topic on which a firm view was expressed was excluded from the findings of the consultation.

Comments on the Council and the Consultation Questionnaire

The systematic analysis of the questionnaire and the additional comments is described below. However, as a significant number of respondents expressed views, critical and otherwise, on both the Council and on the structure and validity of the questionnaire, it is appropriate that these be considered first, as they have a bearing on all that follows. Respondents were invited to express views on whatever topic they wished and, thus, their comments under the present heading, form an important element of the submissions.

The Irish Council for Bioethics

Dealing first with the Council, individual respondents expressed dissatisfaction with the fact that the Council members were appointed rather than elected by the public and that the Council's activities were publicly funded. Some doubts were expressed as to the *bona fides* of the consultation, in particular, that the views expressed by respondents would be ignored. The view was also expressed that the consultation should encompass the representative views of the general Irish public.

The present context is inappropriate to consideration of the constitution of the Council and the comments made in that regard are not addressed in this Appendix, although they have been recorded by the Council. With regard to the consultation itself, there is no question whatsoever of opinions of respondents being ignored. While such an action would be a major breach of faith and wholly unethical, it would also be at odds with the Council's decision to devote both funding and major personnel effort to the arrangements for and the carrying out of the consultation.

On the point of whether the findings would be properly representative of the views of the general public, it is almost inevitable that in such a consultation this would not be the case. (This position is underlined by some of the responses to the preliminary section of the questionnaire, discussed below). To ascertain definitively the opinions of the Irish population on stem cell research would require a rigorously designed and executed survey, preceded by a major information campaign. The Council was anxious to obtain, in a relatively short time, such input as those interested or knowledgeable on the subject were prepared to offer. The exercise—with its limited objectives, as explained earlier—was a success, in that over 2,000 respondents provided information of high value to the Council in the formulation of its Opinion.

Several respondents expressed their appreciation to the Council that their views were sought, with some commenting that the exercise was a valuable one. Some who made submissions emphasised the grave responsibility they considered to rest on the Council on the matter of stem cell research.

The Consultation and the Questionnaire

Several respondents were critical of the holding of the consultation, for various reasons. The views expressed included the following: 1. Ethical issues could not be decided by means of a consultation. 2. There was no point in the exercise, as Ministers had decided to support embryonic stem cell research in the EU. 3. The findings could be skewed by the number of responses being artificially boosted by online campaigners, in particular. On the matter of skewed findings, it has already been noted that given the self selection of respondents, the findings could not be representative of public opinion at large. Rather, the views expressed reflect those of individuals, who were aware of the consultation process and who felt strongly enough about the topic to spend time and effort to submit their views to the Council.

In the matter of the nature and format of the questionnaire, there was a much greater critical response, comprising some 70 submissions in all. These responses related almost exclusively to one or both of two issues: (a) the structure and content of some of the specific questions posed; and (b) whether or not the questionnaire was biased to a greater or lesser extent. In regard to the first point, one of the elements in the preliminary section of the questionnaire was highlighted by several respondents, who queried the relevance or appropriateness of the question on religious beliefs. While it was appreciated that religious beliefs might well have a bearing on the opinions held by members of the public, the respondents in question felt that, information on their beliefs had no place in the consideration of the findings of the consultation. In each of the consultations accompanying previous Council reports, the question on religious beliefs was asked and no attempt has been made in this or previous reports to correlate the existence or not of religious beliefs to responses to specific questions.

Undoubtedly, the more serious criticisms relate to a perceived bias among some respondents on the part of the Council, which was considered by these respondents to favour the introduction of embryonic stem cell research and to have "slanted" the questions accordingly towards the promotion of such research. Some submissions note that Questions 5–9 (10–14)[280] refer only to research or matters involving embryos, underlining the view that there is a deliberate under emphasis on non embryonic research (*i.e.* adult and/or umbilical cord stem cell research). There is disapproval, too, of some of the statements presented for respondents' consideration in Question 10 (15) and of Questions 11–12 (16–17), which, respectively refer to stem cell research, without qualification and to embryonic stem cell research only.

280 The online version of the questionnaire assigns numbers 1–5 to the preliminary questions, which are not numbered in the hard copy (printed) version. In the following discussion, the numbers cited are those in the latter version; the online equivalents are given in parentheses.

The construction of the questionnaire was influenced by the perceived need to bring to public attention those aspects of stem cell research that had proved, or were likely to be, the most problematical. Thus, in Question 4 (9) on embryos from IVF treatment, it was expressly noted that, the use of such embryos would lead to their destruction. A consequence of this approach was the implicit recognition of the absence of similar difficulties with non embryonic stem cell research.

Also, under Question 4 (9) the reference to an embryo acquiring "full moral status" was considered flawed by some respondents, who were unfamiliar with, or had varying interpretations of, the term used.

The purpose of Question 10 (15) was to call attention to some of the frequently used statements, as covered by the media, in regard to stem cell research and to seek views on their validity or otherwise. The reference to "allowing scientists to play God" was considered particularly objectionable. It must be emphasised, however, that none of the six statements presented for comment were necessarily representative of the views of the Council but were included as they have become ubiquitous in the debate on embryonic stem cell research.

Detailed Analysis of the Questionnaire Responses

The Overall Level of Response

The total number of submissions using the provided questionnaire was, as mentioned, just under 2,200—a figure that reflects a high degree of interest in the topic of stem cell research. No fewer than 51% of respondents provided information and comment in the open section following the specific questions. In addition, a further 51 individuals made written submissions which did not involve the use of the questionnaire. As will be noted from the following analysis (undertaken for convenience on a section by section basis), the responses provided the Council with a great deal of valuable input to its consideration of the topic.

Preliminary Section: General Background Information

As with previous questionnaires, the detailed questions were preceded by a section seeking general information on respondents, on an anonymous basis. This information is of value in the overall interpretation of the consultation results, but it is not considered in regard to the specific responses given in any individual submission. Five general topics were covered by this initial section of the questionnaire.

Gender	Response Percent	Response Total
Male	46.9%	1018
Female	53.1%	1151
Total # of respondents 2188. Statistics based on 2169 respondents; 0 filtered; 19 skipped.		

Age Group	Response Percent	Response Total
16–25	16.5%	360
26–35	21.7%	472
36–45	16.5%	360
46–55	13.1%	285
56–65	15.8%	344
66+	16.5%	359
Total # of respondents 2188. Statistics based on 2180 respondents; 0 filtered; 8 skipped.		

Education	Response Percent	Response Total
Primary	1.9%	41
Lower Secondary (JuniorCertificate)	4.4%	95
Upper Secondary (Leaving Certificate)	18.2%	393
Third Level	75.5%	1633
Total # of respondents 2188. Statistics based on 2162 respondents; 0 filtered; 26 skipped.		

Religious Beliefs	Response Percent	Response Total
Yes	83.1%	1798
No	16.9%	365
Total # of respondents 2188. Statistics based on 2163 respondents; 0 filtered; 21 skipped.		

Residence	Response Percent	Response Total
Ireland	95.8%	2075
Other	4.2%	92
Total # of respondents 2188. Statistics based on 2167 respondents; 0 filtered; 25 skipped.		

The level of submissions under these general headings was almost 100%, that is, very few respondents did not make a submission. Undoubtedly, the salient points arising from the responses are, first, the relative uniformity in the level of responses over the six age groups listed and, second, the great preponderance of submissions from those with third level education. It should be noted in the case of the former, however, that the similarity of response totals does not in any way imply a correspondence of viewpoints among those in the various age groups.

The Specific Questions: 1–13

Q1

How much do you know about stem cell research?	Response Percent	Response Total
I know a great deal about it	19.7%	431
I know a fair amount about it	52.4%	1146
I know just a little about it	25.4%	556
I have heard of but know nothing about it	2.3%	51
I have never heard of it	0.2%	4

Total # of respondents 2188. Statistics based on 2188 respondents; 0 filtered; 0 skipped.

It is notable that 72% of respondents had a significant degree of knowledge of stem cell research and that a further 25% were acquainted with the subject.

Q2

Where do you get information on stem cell research? (several boxes may be ticked)	Response Percent	Response Total
Newspapers	72.4%	1575
Television	54%	1176
Radio	40.7%	885
Magazines	36.2%	787
The Internet	43.8%	952
Friends/Family/ Colleagues	47.8%	1040
Other	28.8%	627

Total # of respondents 2188. Statistics based on 2176 respondents; 0 filtered; 12 skipped.

While the high levels of responses covering the principal media are as would be expected, the significant numbers citing magazines and the Internet are less obvious, as is the high figure for "Friends/Family/Colleagues", the latter indicates a considerable level of discussion of the subject among the respondents.

The responses under the "Other" heading included information from religious groups, non governmental organisations and interest groups, as well as information garnered from journals and scientific publications. The term "journal" may be used in regard to publications that may differ greatly in their nature. To a lay person, the term may refer to popular or even partially specialist publications, such as news magazines or periodicals covering matters of current scientific interest, a usage that is quite valid. To the medical or scientific professional, however, the term refers to a "peer reviewed" publication, the contents of which appear only after having been stringently scrutinised by independent experts in the same field of work as the respective authors.

Q3

Have you heard of the following sources of stem cells?	Yes	No	Response Total
Adult human tissue, e.g., hair,skin, bone marrow.	88.2% (1921)	11.8% (257)	2178
Umbilical cord blood collected immediately after birth.	90.3% (1966)	9.7% (212)	2178
Amniotic fluid, i.e., protective fluid surrounding the developing foetus.	68.5% (1493)	31.5% (685)	2178
Foetal tissue obtained from aborted/miscarried foetuses.	83.7% (1822)	16.3% (356)	2178
Human embryos produced, but not used, during *in vitro* fertilisation treatment (IVF)	91.7% (1997)	8.3% (181)	2178
Human embryos produced specifically for research	80.2% (1746)	19.8% (432)	2178
Total # of respondents 2188. Statistics based on 2178 respondents; 0 filtered; 10 skipped.			

Q4

At what point do you believe an embryo acquires full moral status?	Response Percent	Response Total
Fertilisation (i.e., when the sperm and egg join to form an embryo)	69%	1503
When the embryo implants itself in the womb	9.7%	212
At a later time during the pregnancy	11.9%	260
At birth	3.8%	82
Don't know	2.8%	62
Other	2.8%	60

Total # of respondents 2188. Statistics based on 2179 respondents; 0 filtered; 9 skipped.

Of those who answered "Other", one third of the responses reflected the view that moral status was acquired at the point of conception/fertilisation, with one or two of these being a tentative rather than a firm opinion. In contrast, almost half the respondents showed a wide range of opinions, assigning moral status at stages from pre-fertilisation (where there was potential for fertilisation) to birth, including various stages of foetal development.

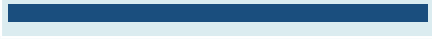
A fifth of respondents were unhappy, either with the use of the term "moral status" (and the lack of a definition of it) or with the nature of the question posed, with some regarding it as being without sense or meaning.

Q5

Do you think it is acceptable to use embryos produced, but not used, during IVF treatment for stem cell research in Ireland? Using these embryos would lead to their destruction.	Response Percent	Response Total
Yes	25.8%	562
No	70.6%	1537
Don't Know	3.5%	77

Total # of respondents 2188. Statistics based on 2176 respondents; 0 filtered; 12 skipped.

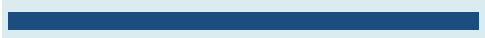
Q6

Do you think it is acceptable to import embryonic stem cell lines into Ireland for stem cell research?		Response Percent	Response Total
Yes		22%	480
No		72.1%	1571
Don't Know		5.8%	127
Total # of respondents 2188. Statistics based on 2178 respondents; 0 filtered; 10 skipped.			

Q7

Do you think it is acceptable to produce cloned embryos as a source of embryonic stem cells?		Response Percent	Response Total
Yes		17.3%	377
No		76.9%	1677
Don't Know		5.9%	128
Total # of respondents 2188. Statistics based on 2182 respondents; 0 filtered; 6 skipped.			

Q8

Do you think it is acceptable to produce cloned human-animal hybrid embryos as a source of embryonic stem cells?		Response Percent	Response Total
Yes		11.3%	247
No		81.2%	1772
Don't Know		7.5%	163
Total # of respondents 2188. Statistics based on 2182 respondents; 0 filtered; 6 skipped.			

Q9

Would you be willing to use medical treatments that were developed using embryonic stem cells?	Response Percent	Response Total
Yes	27.8%	605
No	64.6%	1409
Don't Know	7.6%	166

Total # of respondents 2188. Statistics based on 2180 respondents; 0 filtered; 8 skipped.

Q10

To what extent do you agree/disagree with the following statements?

	Strongly Agree	Moderately Agree	Moderately Disagree	Strongly Disagree	Don't Know	Response Total
(A) Using adult stem cells does not involve the destruction of embryos, therefore scientists should only conduct adult stem cell research.	63.8% (1392)	12% (261)	8.2% (178)	13.9% (303)	2.2% (49)	2183
(B) Scientists should conduct both adult and embryonic stem cell research as we do not currently know which offers more potential for developing medical treatments.	18.4% (401)	9.9% (217)	3.6% (79)	65% (1419)	3.1% (67)	2183
(C) As long as the parents of the embryo give their permission and the embryo would otherwise be allowed to perish, embryonic stem cell research should be permitted on embryos that have not been used for IVF.	22.3% (486)	7.8% (171)	2.9% (63)	64.2% (1401)	2.8% (62)	2183
(D) If scientists believe that embryonic stem cell research will increase our ability to prevent or treat serious diseases, we should trust them and let them do it.	15.2% (331)	10.8% (236)	5% (110)	67.5% (1473)	1.5% (33)	2183
(E) Using cells from human embryos for medical research comes too close to allowing scientists to play God.	54.3% (1186)	11.9% (259)	9.6% (210)	19.4% (423)	4.8% (105)	2183
(F) Allowing any research using stem cells from human embryos should be forbidden because it is unethical and immoral.	62.6% (1366)	3.5% (76)	5.6% (123)	25.1% (548)	3.2% (70)	2183

Total # of respondents 2188. Statistics based on 2183 respondents; 0 filtered; 5 skipped.

Q11

Do you think there is a need for specific legislation concerning stem cell research in Ireland?	Response Percent	Response Total
Yes	84%	1809
No	8%	172
Don't Know	8%	173

Total # of respondents 2188. Statistics based on 2154 respondents; 0 filtered; 34 skipped.

Q12

If embryonic stem cell research were permitted in Ireland, who do you think should be responsible for funding it? (several boxes may be ticked)	Response Percent	Response Total
Government	38%	787
Industry (e.g., pharmaceutical)	24.7%	512
Public/Private partnerships	21.4%	444
Don't Know	16%	332
Other	38.8%	804

Total # of respondents 2188. Statistics based on 2073 respondents; 0 filtered; 115 skipped.

No fewer than 79% of respondents, who answered "Other" in relation to the funding of stem cell research, were of the view that embryonic stem cell research should not be permitted. Some added the comment that given a prohibition, the question of funding would not, therefore, arise. In addition, some respondents noted their clear support for adult stem cell research.

Q13

In relation to stem cell research, what issues would you like to know more about? (several boxes may be ticked)	Response Percent	Response Total
What is the current status of the development of medical treatments using stem cell research?	65.1%	1384
What are the differences between adult and embryonic stem cells?	29.9%	635
What are the potential benefits and risks of adult and embryonic stem cell research?	42%	893
What ethical considerations are raised by stem cell research?	44.6%	949
What stem cell research is taking place in Ireland?	78.5%	1669
Don't Know	2.9%	61
Other	11.7%	249

Total # of respondents 2188. Statistics based on 2127 respondents; 0 filtered; 61 skipped.

Of the respondents who answered "Other", a fifth expressed the view that, there was more than enough information on stem cell research available to them, or that they were sufficiently informed on the subject. However, a smaller (approx. 12%) but significant number of submissions reflected a desire for additional information about the benefits of stem cell research.

Q14: The Open Section

Due to the nature and volume of responses under this heading, they are discussed immediately below in a separate section.

The Number of Submissions

As noted earlier, the "formal" part of the questionnaire—the specific questions posed—was followed by an open section, in which correspondents were invited to add, at will, additional views, comment or information. A total of 1,124 respondents contributed their comments in the open section, thereby adding greatly to the overall value of the consultation.

Analysing the Responses

The rationale behind the open section was that participants in the consultation would have the opportunity to comment, at whatever length and in whatever way they wished, on any aspect of the consultation and/or on any facet of the complex subject being addressed. The sole aim behind this analysis of the submissions was to ascertain, unambiguously, the views of the respondents on the topic(s) they chose to address.

Some submissions were concise, others lengthy and often accompanied by additional explanatory comment. In regard to such supporting material, however, it must be noted that, as explained in the introduction to this Appendix, the only factors taken into account in this analysis were the express views of the respondent. It may be added that the question of the apparent relevance of any particular contribution to the overall subject of the consultation was not considered, as respondents had total freedom in regard to their submissions.

Presentation of the Findings

Despite the individualistic nature of submissions, there were varying degrees of concordance between them, depending on the particular matters being addressed. It was, therefore, practicable to group responses under the following individual headings.

Views For/Against the Different Forms of Stem Cell Research

A total of 55% of the submissions, which made comments in the open section of the questionnaire, addressed this key topic, expressing clear views in regard to stem cell research. The ratio of those opposed to embryonic stem cell research compared to those supporting it was almost 4.5:1 [77% and 17%, respectively]. These findings are discussed below, with consideration of the minority finding first.

Just over 100 respondents expressed their support for embryonic stem cell research. Almost all added the view that such research offered the best hope for the future successful treatment of diseases and disabilities that are currently debilitating or life threatening. However, many of the submissions stated that there should be control safeguards on such work and others expressed reservations about the creation of embryos in the laboratory.

Some 500 submissions expressed opposition to embryonic stem cell research, of which three fifths supported other (non embryonic) forms of stem cell research. The following observations may be made on the above findings. It should also be noted that some of the submissions in favour of embryonic stem cell research (on the grounds of its potential to result in new treatments), have observed that those currently suffering from such illnesses would undoubtedly support such research. Some respondents have indicated thus: but, in contrast, others have maintained their opposition to embryonic stem cell research despite their degraded medical health.

The overall pattern of responses indicates a belief that, adult stem cell research has already revealed its greater potential for the development of new, much needed medical treatments, in contrast to the perceived position of embryonic studies; and the question is repeatedly posed as to why the latter should be pursued at all.

Many of the responses disapproving of embryo based research in which there is destruction of embryos, stress the sanctity of human life—accepted as beginning at conception—and several make the point that it is not morally justifiable to destroy one human life for the purpose of preserving another. The creation of embryos for the purposes of laboratory research is specifically condemned by some respondents.

Views on Control Of Stem Cell Research (Including the Need for Legislation)

Respondents agreed that strict control or monitoring of stem cell research is essential, although they differ as to whether this control should be statutory or not. Most opinions favour the establishment of an authoritative committee or expert group, with membership exclusive of those with vested interests. It was suggested that, such a group would probably be best set up by the State, which should fund it properly. It would have the task of monitoring all stem cell research, in both the private and public sectors, if it were to assist Ireland to compete internationally, it should be established by statute.

Individual respondents, respectively, suggested that the nature of this controlling body should be similar to that in the UK; that its regulatory procedures should be in line with those of other countries so as to allow the prompt use of results of successful research; that the membership of the group should include lay persons as well as professional experts; that a moral framework is required within which this body would operate; and that there should be guidelines for researchers, which would be made available to the public.

Express comments on the need for legislation governing embryonic stem cell research fall into two groups, although they share a similar philosophical background. The first set of comments asserts that there should be "womb to tomb" legislation in order to protect embryos in the first instance; while the second suggests that, as there is current protection under the Constitution, a further law is unnecessary. One other response calls for legislation to prevent embryonic stem cell research, the destruction of embryos and IVF.

Views on Embryo Related Matters Other Than Stem Cell Research

Submissions in this category covered: (*i*) the importation of embryos; (*ii*) the creation by scientists of human-animal hybrid embryos; (*iii*) IVF and the question of when human life begins. Few specific comments were made in regard to the importation of embryos from other countries or to the creation of human-animal hybrid embryos. All respondents were uniformly opposed to both, with the sole exception of a submission that countenanced the importation of frozen embryos from foreign countries with ethical standards corresponding to those in Ireland.

Likewise, there was relatively little mention of IVF as such in the submissions. The small number of responses that did consider the matter fell into the following categories: (a) those opposed to IVF *per se* and those concerned especially about the fate or use of "surplus" (*i.e.* supernumerary) embryos; (b) those that felt such supernumerary embryos should be used beneficially for research rather than being destroyed, including one submission noting that the "parents of unused embryos" had the right to decide on their future use; and (c) single submissions that, respectively, wished for a degree of control of IVF using the system currently in use in Germany and that stated that the whole debate should expressly include IVF, in connection with which there were difficult questions.

In contrast, the belief that life begins at conception/fertilisation pervades the submissions in this consultation and references are too many to discuss. It should be noted, however, that some responses state unequivocally that, science (as distinct from personal beliefs) declares it as fact that conception is the start of life. One respondent has expressed the view that, there should be an unequivocal legal definition as to when life begins, as a pre-requisite for proper control of research.

Views on Forms of and Future Direction of Stem Cell Research

Respondents initially examined the benefits and problems, perceived or actual, of adult and embryonic stem cell research—the two principal forms of this research. There is a general view that there are moral problems with embryonic research, which involves the destruction of the embryo; and this view is accompanied by a universal opinion that no such difficulties arise with adult stem cell research. Embryonic stem cell research is stated to be the easier and cheaper option, but some submissions are doubtful about its efficacy and safety, and others consider that embryonic stem cell studies are not at a stage where it is clear that any treatment benefits will accrue. Some respondents maintained that embryonic stem cells are too unstable for clinical trials.

Although the view is expressed that both adult and embryonic stem cell research are equally effective, there is a contrary view that asks whether any patient treated with either adult or embryonic stem cells has, to date, benefited from treatment. However, this represents a minority viewpoint. While some contributors acknowledged the more complex nature of adult stem cell research, most submissions clearly considered adult stem cell studies to have been proven successful in affording effective treatment possibilities. It was also a view among respondents that should the operational drawbacks of adult stem cell research be eliminated, there would be no need for embryonic stem cell studies. However, some respondents expressed support for embryonic stem cell studies on the basis that this research seems the more promising for treatment development.

Several respondents referred to the production of stem cells from umbilical cord blood and associated sources, querying why embryonic/foetal cells are required when such other sources are available. For some, umbilical cord stem cells offer as great a potential for research as adult stem cells. Those referring to umbilical cord stem cells in their submissions generally added the view that it is wrong—medically, morally and practically—for hospitals not to collect umbilical cord stem cells following births.

The potential benefits from and the possible direction of future research is addressed in several submissions, which take a positive view on the potential value of continuing research; although it is not always clear in these submissions if embryonic stem cell studies are included or not. Overall, stem cell research is seen as having great promise for the development of cures for genetic diseases. It is regarded as a positive development, if legislated for properly; and some consider it the only way forward for patients with crippling diseases. One respondent comments that, while research with adult stem cells offers great promise, for some conditions—spinal cord damage is cited—embryonic stem cells are preferable. However, this submission—along with one that states that recent results with adult stem cells were “unrepeatable and unsubstantiated”—holds that because of uncertainties, there should be proper funding of both adult and embryonic stem cell research.

Views on the Funding of Any Stem Cell Research Approved in Ireland

Opinions on the source of funding of any stem cell research that may be carried out in Ireland were wide ranging. What is quite clear overall, however, is the view that all funding should be public, without financing or control by the private sector. Both direct funding by Government and possibly by public–private partnership were suggested. In contrast, several respondents are adamant that, "taxpayers' money should not go to stem cell research". Respondents in favour of public funding take the view that, such financial support should relate to adult stem cell research only and not to embryonic stem cell research. One contributor notes that, industry is anxious for public funding of adult stem cell research, as this research is potentially risky in financial terms.

Some respondents comment without favour on the perceived availability of industry funding for embryonic stem cell research; and on the consequent attraction of such funding both for researchers anxious to obtain grants and for the Government, which is anxious to encourage the establishment of multinational research centres in Ireland.

Views on the Irish Council for Bioethics

Those submissions critical of the Council and/or the consultation have been addressed earlier and it remains simply to note the remaining comments made on the Council. Some 30 respondents expressed their appreciation that the Council had held the consultation, as it either brought the topic to their attention and/or afforded them the opportunity of presenting their views. Other submissions stated the reservation that, a sampling of public opinion was not a guarantee of an ethical outcome. There was concern, too, about the perceived limited availability or circulation of the questionnaire. Further, several contributors expressed the hope that the Council would promote ethical research, with one requesting that the Council would explicitly reject all non therapeutic embryo research.

Views on Lack of and Need for Information on Stem Cell Research

Notwithstanding the responses to Question No. 1, indicating quite a wide degree of knowledge on stem cell research on the part of contributors, a considerable degree of confusion arises from the indiscriminate use of the non specific term "stem cell research" to cover either embryonic or non embryonic [adult] or both forms of such research. One submission adds that, some confuse embryonic stem cell research with abortion.

In addition to loose terminology, respondents are concerned about the perceived huge amount of misinformation that clouds the matter greatly. Some (non official) publicity campaigns are seen to trade on the lack of knowledge of the public at large on anything to do with research in general and on stem cell research, in particular, leading to what one respondent terms a "knee-jerk reaction" to such research.

Above all, the submissions call for an education campaign—one that is informative and unbiased—followed by a public debate on a National basis. It is considered that such an approach would be most helpful to the general public and to politicians, whose current state of knowledge on stem cell research is not perceived to be adequate. Respondents consider that, the media should play its part by adopting greater accuracy in its use of terminology and by taking a more even handed approach in reporting on all aspects of stem cell research.

Several respondents highlight the topics on which they feel complete, unbiased information should be provided; one suggested that, the data should be disseminated by a comprehensive (though unspecified) effort and not simply by leaflet distribution through the postal system. Another argued that, the provision of information to the public should be undertaken by communications, rather than scientific, experts. Suggested topics on which information should be provided include: the current state of stem cell research both nationally and internationally; the ethical, medical and scientific aspects and implications of the different forms of stem cell research; and the background to the development of IVF.

With respect to the structure of the debate, respondents call for discussion on a rational basis, devoid of emotional arguments, in which openness is essential, as it is felt that fear of any "cover-up" would heighten public anxiety. It is thought vital that people are informed fully on all aspects of stem cell research, with the observation being made that, the Irish population is not stupid and is quite capable of deciding issues on the basis of valid information. One respondent is concerned lest the debate focus solely on embryonic rather than all stem cell research; while another is of the view that the only research that should be permitted and funded is that which the whole community is united in supporting.

Points that two respondents consider important in the debate are that, when considering matters of fundamental ethics, issues such as the ease or otherwise of particular types of research and the state of National economics are not relevant and should not be taken into consideration.

Views on Politics and Electoral Matters

A small number submissions touch on political matters, with respondents hoping that politics will be left out of the debate and noting the lack of understanding of stem cell research on the part of politicians. Another view summarises the opinions of several respondents—the protection of ethical principles is an electoral matter and society must take whatever decisions are required. This implies the holding of a referendum, which is expressly called for by other submissions on this topic.

Views on Religious Beliefs

Opinions regarding the relevance or appropriateness of the preliminary section question on respondents' religious beliefs have been discussed earlier. However, further comments were made on this topic in several of the submissions, which fell into two subgroups. The first took the broad view that religious beliefs or dogma should be left out of the debate and/or should not dictate the terms of scientific progress or of public policy. One respondent asked that religion and politics be kept out of consideration, while another stated that the question of embryonic stem cell research could not be left to the churches or scientists. The second group expressed the fear that those with religious convictions might be discredited, noting that religious/ethical views should not be discounted for the sake of scientific experimentation. Another view was that stem cell research should proceed in accordance with the beliefs of the Catholic Church.

Views on Role and Responsibility of Government

The submissions considered under this heading are those that commented on specific topics that it was considered were matters for Governmental attention, although it may be noted that many other responses contained passing references to the same matters. Further, some of the observations in consideration here will have been touched on elsewhere in this Appendix, but it is useful to collate them here.

The range of views expressed in matters concerning Government is perhaps the widest in the consultation; it is possible, however, to classify them as follows:

(a) criticism of Governmental and Ministerial action and/or inaction;

(b) views for and against the State funding of stem cell research (any form);

(c) the consequent need for Governmental control of such research;

(d) the suggestion that the Government should take a proactive role in establishing Ireland as a European leader in such research;

(e) views that the Government should ban research on embryonic stem cell research; and

(f) the suggestion that consideration of views held by other countries not be limited to or overly influenced by the UK or the US.

Under (a), there is dissatisfaction among respondents that the Government has not instituted a public debate on stem cell research, it being considered that there is an obligation on the State to inform people fully on all issues in the matter and to consider public opinions fairly. The Government is criticised by some respondents for approving the contribution of National funds towards embryonic stem cell research in the EU. Irish members of the European Parliament are likewise criticised for their perceived support of embryonic stem cell research, again without reference to or knowledge of the public. Respondents are also disapproving of the National media for very restricted reporting of developments in regard to stem cell research in the EU.

The salient opinion as regards funding—(b) above—is that a clear majority of submissions favour State funding of adult stem cell research only. On the matter of control, (c) above, also discussed earlier, respondents are clear that the Government should exert tight control of stem cell research, with one respondent adding that the State should regulate both AHR and embryonic stem cell research. In some submissions, a role is seen for the Government to take an initiative (d) in regard to stem cell research (perhaps embryonic) and to develop Ireland as a leading research base.

Throughout the submissions overall, there is a minority view that international developments (f) and their implications for Ireland should be both taken into account by the Government and brought to the attention of the public. One contributor suggests that the position in other European countries, in particular, be investigated and that no undue emphasis should be placed on current thinking in the UK and the US. Finally, the Government is reminded of its responsibility to protect human life and in this regard it is asked to define by legislation when exactly such life begins.

Views on Role of the Pharmaceutical Industry and Patenting

The submissions are unambiguous in holding that the pharmaceutical industry should have no part in the governance of stem cell research, as its primary concern is perceived to be generating profit. Contributors were of the view that, pharmaceutical companies did not foresee a commercial return from adult stem cell research (in view of its greater complexity) and were, therefore, exerting maximum pressure for the introduction of the more straightforward and potentially very profitable embryonic stem cell research. Another reason cited as to why the industry should not have an involvement in overseeing the governance of stem cell research was the urgency for the industry to discover new medications, as existing drugs lost their effectiveness or as the patents governing them expired. It may be noted in the latter connection that respondents were against the patenting of treatments derived from stem cell research.

Views on Scientists

Although the opinions on scientists expressed in the responses submitted by participants vary, there is an underlying view that the scientific community should operate under definite restraints. One respondent is of the view that decisions in regard to embryonic stem cell research cannot be left to scientists. It is suggested that without controls, scientists can exceed ethical boundaries; and some respondents would not trust them on moral issues. However, one respondent feels it unfair that scientists should be put in the position of moralists. A key issue is how scientists respect human life and one suggestion is that the ethical standards of all scientists and researchers should be verified. In any event, respondents believe that scientists should be ethically accountable.

Conclusion

Thanks to the freely offered opinions of respondents, this open element of the consultation has proved a very valuable input to the Council in its work on stem cell research. No summary is added here—the key findings stand clear of the others and the supplementary findings, because of their breadth and diversity, do not lend themselves to further contraction.

Acknowledgements

The Irish Council for Bioethics is most grateful to all respondents to this important consultation and it is very appreciative of the time and thought expended on the many submissions. It is clear from the preceding pages of this Opinion that a great deal of comment, information and personal viewpoints has been presented to the Council, whose deliberations will, thereby, be greatly assisted.

Appendix B: Public Consultation Advertising and Publicity

Advertising

Date	Newspaper
5th March 2007	Irish Times
5th March 2007	Irish Independent
5th March 2007	Irish Examiner
5th March 2007	Belfast Telegraph
March – April 2007	Irish Council for Bioethics' Website

Publicity: Radio

Date	Programme	Interviewee
8th March 2007	Today with Pat Kenny, RTÉ 1	Dr. Siobhán O'Sullivan
7th March 2007	Limerick Today, Live 95 FM	Dr. Siobhán O'Sullivan
5th March 2007	The Right Hook, Newstalk 106	Dr. Siobhán O'Sullivan

Publicity: Print/Web

Date	Publication	Interviewee/ Author/Source	Topic/Title
30th April 2007	Family & Life	Website News	"Irish Bioethics Council's Public Consultation Criticised"
26th April 2007	Irish Catholic	Maree Quinn	"The Deadline for Submissions to the Irish Bioethics Council Stem Cell Research is Fast Approaching"
20th April 2007	Irish Family Press	News Piece	"Deadline Approaches for Pro-Life Submissions"
April Edition 2007	Alive!	Editorial & News Piece	"What's Behind this Bioethics Survey?"
19th April 2007	REMEDI	Website News	"Irish Council for Bioethics Stem Cell Research Public Consultation"
18th April 2007	Family & Life	LifeZine	"Irish Council for Bioethics Survey Under the Spotlight"
21st March 2007	Irish Examiner	Evelyn Ring	"Strong Response to Questions Over Embryo Research"
15th March 2007	Irish Times	Patsy McGarry	"Bishops Urge Involvement in Stem Cell Research Debate"
12th March 2007	Irish Times	Editorial	"Stem Cell Research"
7th March 2007	Family & Life	LifeZine	"Irish Bioethics Council Asks Public for Views on Stem Cell Research"
6th March 2007	Irish Examiner	Dr. Siobhán O'Sullivan/ Caroline O'Doherty	"Give Your Views on the Ethics of Research Using Embryos"
6th March 2007	Irish Times	Dr. Siobhán O'Sullivan/ Dick Ahlstrom	"Public Asked for Views on Stem Cell Research"
5th March 2007	Irish Independent	Eilish O'Regan	"Public to Get Their Say on Stem Cell Research"
4th March 2007	Irishhealth.com	Website	"Public Asked About Stem Cell Research"
4th March 2007	The Multiple Sclerosis Resource Centre	Website News	"The Irish Public is Being Asked to Give its Opinions on Stem Cell Research"

Appendix C: Submissions Sought by the Irish Council for Bioethics

The following is a list of the organisations from which the Irish Council for Bioethics sought submissions.

An Bord Altranais
Bar Council
Chief Rabbinate of Ireland
Church of Ireland General Synod
Disability Federation of Ireland
Family & Life
Genetic & Inherited Disorders Organisation
Health Research Board
Humanist Association of Ireland
Institute of Obstetricians and Gynaecologists of the Royal College of Physicians of Ireland
Irish BioIndustry Association
Irish Bishops' Committee for Bioethics
Irish College of General Practitioners
Irish Council of Imams
Irish Fertility Society
Irish Network of Neural Stem-Cell Investigators
Irish Patients' Association
Law Reform Commission
Law Society of Ireland
Medical Council
Medical Research Charities Group
Methodist Church in Ireland
National Infertility Support and Information Group
Neurological Alliance of Ireland
Presbyterian Church in Ireland
Pro-Life Campaign
Science Foundation Ireland
Youth Defence

Appendix D: Submissions Received by the Irish Council for Bioethics

The following is a list of the oral and/or written submissions received by the Irish Council for Bioethics

An Bord Altranais

Bar Council

Chief Rabbinate of Ireland

Church of Ireland General Synod

Family & Life

Genetic & Inherited Disorders Organisation

Health Research Board

Humanist Association of Ireland

Institute of Obstetricians and Gynaecologists of the Royal College of Physicians of Ireland

Irish BioIndustry Association

Irish Bishops' Committee for Bioethics

Irish Council of Imams

Irish Fertility Society

Irish Network of Neural Stem-Cell Investigators

Irish Patients' Association

Medical Council

Medical Research Charities Group

Methodist Church in Ireland

National Infertility Support and Information Group

Neurological Alliance of Ireland

Pro-Life Campaign

Science Foundation Ireland

Youth Defence

Appendix E: Overview of the Legislation on/ Regulation of Stem Cell Research Globally

Legislation/Regulation in EU Member States

Within Europe, despite the variation in the specific regulations and guidelines relating to research involving embryos and embryonic stem cells, countries can generally be grouped together on the basis of the stringency of their legislation.[281,282] The countries are listed below in order of increasingly restrictive legislation with regard to research involving embryos and embryonic stem cells.

In the UK, under the *Human Fertilisation and Embryology Act* (1990),[283] it is legal to conduct research on embryos, including the derivation of embryonic stem cells. The use of embryos in research is only allowed during the first 14 days of development and keeping or using an embryo after that period is prohibited by the legislation. The HFEA was established in 1991 to regulate IVF clinics, donor insemination and embryo research through the granting of licences. It should be noted that, once embryonic stem cell lines have been developed they are no longer considered embryos and, therefore, cannot be regulated by the HFEA. Guidance and assistance on the ethics and best practice in the use of these isolated embryonic stem cell lines is provided by the Steering Committee of the UK Stem Cell Bank.[284]

The 1990 Act allowed, in very limited circumstances, the creation of embryos by IVF and SCNT. In 2001, the *Human Fertilisation and Embryology (Research Purposes) Regulations* were enacted. These extended the purposes for which an embryo could be created, not for reproduction, but for research, to increase knowledge about serious disease and to enable such knowledge to be applied in developing treatments for such diseases. Following the introduction of the Regulations in 2001, an application was made by the ProLife Alliance for a judicial review of the legislation with specific reference to the status of the embryo created by SCNT. The High Court agreed with ProLife that cloned embryos did not come under the 1990 Act, as such embryos are not created by "fertilisation" as defined in the original Act. As a result of the ruling, concerns were expressed that a legal loophole existed that would permit reproductive cloning. Thus, the UK Government introduced legislation *(The Human Reproductive Cloning Act)* that makes the implantation of a cloned embryo into a woman a criminal offence.[285]

281 Fagniez (2006) *op. cit*. provides a thorough review of the national positions adopted in relation to stem cell research worldwide.

282 International Consortium of Stem Cell Networks (last updated December 2007) *Global Regulation of Human Embryonic Stem Cell Research and Oocyte Donation*. Available online at: http://icscn.files.wordpress.com/2007/12/global-regulation-hesc-research-oocyte-donation-dec-07.pdf, accessed 18 March 2008.

283 *Human Fertilisation and Embryology Act* (1990), Chapter 37. Available online at: http://www.opsi.gov.uk/acts/acts1990/Ukpga _ 19900037 _ en _ 1. htm, accessed 7 December 2007.

284 UK Stem Cell Bank (2006) *Code of Practice for the use of Human Stem Cell Lines*. Hertfordshire, England.

285 *Human Reproductive Cloning Act* (2001), Chapter 23, Available online at: http://www.opsi.gov.uk/acts/acts2001/pdf/ukpga _ 20010023 _ en.pdf, accessed 28 September 2007.

In 2002, the Government successfully appealed against the aforementioned initial High Court decision and the Court of Appeal ruled that an embryo created by SCNT did fall within the definition of the 1990 Act. This position was further supported by a House of Lords judgment in 2003, which found in favour of the Government. In 2004, the HFEA granted the first licence to create human embryonic stem cells using SCNT.[286]

In May 2007, following a review of the *Human Fertilisation and Embryology (Research Purposes) Regulations* (2001), the UK Government published a draft of the *Human Tissue and Embryos (Draft) Bill*.[287] The purpose of the Bill is to revise the law on AHR and embryology, and to establish a Regulatory Authority for Tissue and Embryos. As a result of reccomendations made by a House of Commons Science and Technology Committee,[288] the Bill allows for the creation of human-animal hybrids (an embryo created by replacing the nucleus of an animal egg with a human cell) for research purposes. On 5 September 2007, the HFEA agreed in principle to licence the creation of human-animal hybrid embryos for stem cell isolation and medical research into debilitating diseases. "This is not a total green light for cytoplasmic hybrid research, but recognition that this area of research can, with caution and careful scrutiny, be permitted".[289]

Similarly to the UK, a number of other countries also allow the creation of embryos for research purposes. For example, in Belgium, under the *Law on Research on Embryos In Vitro* (2003), embryos can be created for research if the proposed research cannot be conducted using supernumerary embryos and provided the research meets the normal criteria for embryo research. These criteria include the stipulation that the research is conducted during the first 14 days of development (not counting time in storage) and that the research has a therapeutic purpose or the potential to improve medical knowledge.[290] Moreover, embryo research requires approval from the relevant local ethics committee and from the Belgian Federal Commission for medical and scientific research on embryos *in vitro* before it can begin.

In Sweden, research involving embryos and embryonic stem cells has been allowed since 1991 under the *Act on Measures for Purposes of Research and Treatment using Fertilized Human Ova*. Under this legislation, research can be conducted on embryos during the first 14 days of development, following donor consent and subject to approval by the regional research ethics authority. A number of other regulatory instruments relating to embryo research have been implemented since 1991,[291] the most recent of which superseded the 1991 Act.[292] Under the current legislation, it is now legal to create embryos for use in research and for the procurement of stem cells, which includes allowing SCNT for therapeutic purposes.[293]

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286 Human Fertilisation & Embryology Authority (2004) *HFEA grants the first therapeutic cloning licence for research*. Press release, published 11 August 2004. Available online at: http://www.hfea.gov.uk/en/1048.html, accessed 28 September 2007.

287 *Human Tissue and Embryos (Draft) Bill* (2007). Available online at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsLegislation/DH _ 074718, accessed 28 September 2007.

288 House of Commons Science and Technology Committee (2007) *op. cit*.

289 Human Fertilisation & Embryology Authority (2007) *HFEA statement on its decision regarding hybrid embryos*. Published 5 September 2007. Available online at: http://www.hfea.gov.uk/en/1581.html, accessed 26 September 2007.

290 Pennings G (2003) New Belgian Law on Research on Human Embryos: Trust in Progress Through Medical Science. *J Assist Reprod Genet* 20(8): 343–346.

291 *The Transplantation Act* (1995:831); and *The Biobanks in Medical Care Act* (2002:297).

292 *The Act concerning the Ethical Review of Research involving Humans* (2003:460); and *the Genetic Integrity Act* (2006:351).

293 *The Genetic Integrity Act* (2006:351).

Spain is the most recent country in Europe to allow the creation of embryos for use in research.[294] A number of other acts also regulate research involving embryos, which includes supernumerary IVF embryos, cloned embryos and embryonic stem cells.[295] These regulations require that the embryos used have undergone less than 14 days of development and that the research has been approved by the relevant commission,[296] as well as the local research ethics committee and any other relevant authority.[297]

While not permitting the creation of embryos for use in research, several other European countries allow research using embryonic stem cells derived from supernumerary IVF embryos. These countries include the Czech Republic,[298] Denmark,[299] Finland,[300] France,[301] Greece,[302] Hungary,[303] the Netherlands,[304] Portugal,[305] Slovenia[306] and Switzerland.[307] In the countries listed, various criteria need to be adhered to in order to conduct research on embryos and/or embryonic stem cells, such as: the consent of the donors of the embryo must be obtained; the research can only be carried out on embryos during the first 14 days of development; the embryos involved can no longer be used for reproductive purposes; the research should offer potential improvements to science and/or medicine; no alternative methods of reaching the desired research outcome should be available; only authorised institutions/licensed research groups can conduct the research; all research must be approved by the appropriate National authority and/or the relevant research ethics body.[308]

Nevertheless, the situation regarding research involving embryos and embryonic stem cells in a number of these countries requires further clarification, particularly with regard to SCNT. For example, in the Netherlands under the *Embryos Act* (2002), a moratorium of indefinite duration is in place, which prevents the creation of embryos specifically for research purposes, including through the use of SCNT. The Act states that the moratorium can be lifted at a time to be decided by Royal Decree.

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294 European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit.*

295 These acts are the *Human Assisted Reproduction Techniques Act* (2006) and the *Biomedical Research Act* (2007).

296 Research relating to the application and implementation of human assisted reproductive techniques requires the approval of the National Commission on Assisted Human Reproduction, whereas research relating to the creation, implementation and use of human embryonic stem cell lines must be approved by the Commission for Establishing Guarantees in the donation and use of human cells and tissues.

297 European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit.*

298 In the Czech Republic, research on embryonic stem cells is governed by the *Act on Human Embryonic Stem Cell Research* (2006).

299 In Denmark, research involving embryos and embryonic stem cells is governed by *Lovbekendtgørelse af lov om kunstig befrugtning i forbindelse med lægelig behandling,diagnostic og forskning* (LBK nr. 923 af 04//09/2006).

300 In Finland, research involving embryos is governed by the *Medical Research Act* (488/1999). An unofficial translation of this act is available online at: http://www.finlex.fi/en/laki/kaannokset/1999/en19990488.pdf, accessed 10 December 2007.

301 Le décret n°2006–121 du 6 février 2006 and la loi n°2004–800 de bioéthique du 6 aout 2004.

302 In Greece, research involving embryos is governed under the Civil Code by *Law 3089 (2002) Medically Assisted Human Reproduction*. Available online at: http://www.bioethics.gr/media/pdf/biolaw/human/law _ 3089 _ en.pdf?PHPSESSID=c730cd74d93449cca3750bb51c50a228, accessed 10 December 2007, and also by *Act 3305 (2005) on the Application of Medically Assisted Reproduction*.

303 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit.*, p.84.

304 *Embryos Act* (2002). Available online at: http://www.minvws.nl/images/eng-embryowettekst _ tcm20–107819.pdf, accessed 7 December 2007.

305 *Law (32/2006) Concerning Medically Assisted Reproduction* addresses human embryonic stem-cell research.

306 *The Law on Treatment of Infertility and Biomedically Assisted Fertilisation* (2000) contains provisions that apply to research on embryos from IVF procedures and may apply to procurement of human embryonic stem cells.

307 *Federal Act on Research on Surplus Embryos and Embryonic Stem Cells (Embryonic Research Act)* (2004).

308 For a detailed breakdown of the legislation and regulation applicable in each country, see the European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit.*

It should be noted that the *Embryos Act* (2002) was brought into force with the intention of eventually allowing the creation of embryos for research (including using SCNT) and, therefore, the Act already contains provisions for the regulation of such practices. In 2006, a committee established to review the *Embryos Act* recommended that the moratorium on creating embryos for research should be lifted.[309] Nonetheless, no formal Government decision about ending or extending this moratorium has been taken, as yet.[310] A potential conflict could arise in this regard, since the Netherlands has signed (though not yet ratified) the *European Convention on Human Rights and Biomedicine* (1997), which prohibits the creation of embryos for research purposes.

In Finland, the *Medical Research Act* (1999) prohibits the creation of embryos exclusively for research. However, this Act also defines an embryo as "a living group of cells resulting from fertilisation not implanted in a woman's body".[311,312] It has been suggested that this wording could be interpreted to mean that cells produced *via* SCNT are not considered as embryos[313] and, therefore, could potentially be used in research.

It should be noted that in Estonia, under the *Embryo Protection and Artificial Fertilisation Act* (1997), research can be conducted on supernumerary embryos. However, there is no specific legislation dealing with embryonic stem cell research; although the Estonian Council on Bioethics has suggested that such research should be allowed.[314]

In France, the *Bioethics Law* (La loi n°2004–800 de bioéthique du 6 aout 2004) forbids the creation of embryos for research or therapy. However, in preparation of the 2009 revision of the *Bioethics Law*, a parliamentary mission published the Fagniez report, *Stem cells and ethical choices* (*Cellules souches et choix éthiques*), in July 2006. This report recommends allowing research on supernumerary embryos and lifting the prohibition on cloning for research purposes.[315] The French National Advisory Ethics Committee for Health and Life Sciences has reported in favour of embryonic stem cell research and SCNT.[316,317] The French National Advisory Commission on Human Rights (La Commission Nationale Consultative des Droits de l'Homme) is supportive of embryonic stem cell research, but not SCNT.[318] The French academies of science and medicine have released a joint statement in favour of embryonic stem cell research and SCNT.[319]

309 Olsthoorn-Heim ETM, de Wert GMWR, Winter HB, te Braake ThAM, Heineman MJ, Middelkamp A and Nierse CJ (2006) *Evaluation Embryos Act*. The Hague, p.9. Available online at: http://www.zonmw.nl/fileadmin/cm/vraagsturing/documenten/Evaluatie _ regelgeving/embryos _ act _ en _ sum.pdf, accessed 7 December 2007.

310 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*.

311 *Medical Research Act* (488/1999) *op. cit*.

312 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*.

313 *ibid*.

314 *ibid*.

315 Fagniez (2006) *op. cit*.

316 French National Advisory Ethics Committee for Health and Life Sciences (1986) *Opinion on research and use of in-vitro human embryos for scientific and medical purposes. Report.* Opinion No.8. Paris.

317 French National Advisory Ethics Committee for Health and Life Sciences (1997) *Reply to the President of the French Republic on the subject of reproductive cloning.* Opinion No.54. Paris.

318 Commission Nationale Consultative des Droits de l'Homme (2001) *Avis portant sur l'avant-projet de loi tendant à la révision des lois relatives à l'éthique biomédicale*. Paris.

319 French Academy of Sciences and the National Academy of Medicine (2002) *Recommendations of the Academy of Sciences and of the National Academy of Medicine regarding the use of human embryonic stem cells*. Paris.

In a number of European countries research on embryos, including the derivation of embryonic stem cells, is more restricted. For example, in Germany, the *Embryo Protection Act* (1990) does not permit the use of embryos in research, whether to procure stem cells or otherwise. However, this Law did not specifically exclude the importation of embryonic stem cell lines. A more recent law, the *Stem Cell Act* (2002), maintains the ban on producing embryonic stem cell lines in Germany but it allows embryonic stem cell lines to be imported under certain conditions. These conditions include stipulations that: the imported embryonic stem cells were derived prior to 1 January 2002 in their country of origin; the embryos from which the stem cells were derived were produced, but not used, for infertility treatment; the research involving the embryonic stem cells aims to improve scientific and/or medical knowledge, *e.g.* through the development of therapies; and the aims of the research project could not be achieved without using embryonic stem cells. Furthermore, in all cases the Central Ethics Committee for Stem Cell Research at the Robert Koch Institute (Berlin) must approve the importation.[320]

The creation of embryos for research is also banned in Italy under the *Law* (40 of 2004) *on Medically Assisted Reproduction*. In addition, this Law prohibits research on supernumerary IVF or SCNT embryos (and, therefore, prohibits the derivation of embryonic stem cells). However, there are no legal regulations with regard to the use of imported or existing human embryonic stem cells. An attempt was made in 2005 to make a number of changes to the *Law on Medically Assisted Reproduction*, including allowing embryonic stem cell research. A referendum was held to amend the Law, however, this was unsuccessful because the voter turnout did not reach the required quorum. It has been suggested that the low voter turnout was, at least partly, due to the influence of the Catholic Church. Prior to the referendum, the Catholic Church, with the backing of Pope Benedict *XVI*, had called for Italian citizens to abstain from voting.

A number of other European countries have also restricted, by law, research involving embryos and embryonic stem cells. In Austria, the *Reproductive Medicine Act* (1992) states that cells capable of development can only be used for reproductive purposes, which would, therefore, preclude the procurement of embryonic stem cells from embryonic tissues.[321,322,323] However, the use of imported human embryonic stem cells is not explicitly forbidden and a discussion of this issue is currently taking place. In Norway, while research on embryos had been banned since 1994, an amendment to the law in 2003 explicitly prohibited research using embryonic stem cells and cloning for research purposes.[324] In Lithuania, despite the lack of specific legislation relating to embryonic stem cells, such research is effectively banned under the *Law on Ethics of Biomedical Research* (2000), which forbids all research on human embryos apart from observational studies. In addition, the Slovak Republic prohibits any "non therapeutic" research to be conducted on embryos and also bans both

320 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*.

321 European Commission Directorate General: Research (2003a) *Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use. Volume I in EU Member States*. May 2003, Brussels, p.17.

322 Commission of the European Communities (2003) *Commission Staff Working Paper. Report on Human Embryonic Stem Cell Research*. SEC(2003) 441, Brussels.

323 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*.

324 Act of 5 December 2003 No. 100 relating to the application of biotechnology in human medicine, etc (The Biotechnology Act). Available online at: http://www.ub.uio.no/ujur/ulovdata/lov-20031205–100-eng.pdf

reproductive and research cloning.[325] More detailed legislation is being prepared, which may include regulations regarding embryonic stem cell research, which the Slovak Government voted against during the European Council decision for FP7.[326] In Cyprus, there is no specific law to allow research on *in vitro* embryos, but embryonic stem cell research is not permitted.[327] Finally, in Poland, all research involving embryos is prohibited.[328]

However, it should be noted that, similarly to Ireland, a number of European countries, including Latvia, Luxembourg,[329] Malta and Romania, have no specific legislation relating to research involving embryos and/or embryonic stem cells. Therefore, the legal status of such research is somewhat unclear.

Legislation/Regulation in the Americas

The situation regarding research on embryos and embryonic stem cells in the US is somewhat complicated, due to the different positions taken at the Federal and individual state levels. There is no Federal legislation regulating embryonic stem cell research and human cloning, *i.e.* conducting such research is neither prohibited nor encouraged by the Government.[330] However, legislation is in place that controls the allocation of Federal funding to embryonic stem cell research.

Despite support from President Clinton to allow Federal funding of research involving embryos, in 1995 Congress banned the use of any Federal funds for research in which embryos would be destroyed and for the creation of human embryos for research purposes. However, when human embryonic stem cells were isolated, the US National Institutes of Health (NIH), the Federal Government's primary sponsor of biomedical research, sought legal counsel from the Department of Health and Human Services as to whether the ban on funding human embryo research would apply to embryonic stem cell research. In January 1999, the Department of Health and Human Services concluded that public funds could be used for research on human embryonic stem cells, as long as the derivation of the cells was carried out with private funds. In 2000 the NIH, with the support of President Clinton, produced guidelines relating to Federally funded research on human embryonic stem cell lines established in the private sector from supernumerary IVF embryos and donated with the consent of the parents.

325 European Commission Directorate General: Research (2003b) *Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use. Volume II Countries acceding to the EU, Countries associated to FP6 and Third countries*. May 2003, Brussels, p.24.

326 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*.

327 European Commission Directorate General: Research (2003b) *op. cit*., p.17.

328 The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*. p.99.

329 In Luxembourg, legislation is in preparation. See The European Group on Ethics in Science and New Technologies to the European Commission (2007) *op. cit*. p.93.

330 The President's Council on Bioethics (2004a) *op. cit*.

However, following the election of President Bush in 2000, the NIH guidelines were put on hold, pending a review.[331,332] Following the review, President Bush decided that Federal funding could be allocated to research involving embryonic stem cell lines derived before 9 August 2001, provided other conditions were also met. Nonetheless, this decision upheld the ban on funding the creation of embryos for research purposes and on cloning human embryos for any purpose. However, the funding of such research in the private sector was still possible. Following President Bush's decision, the NIH established the Human Embryonic Stem Cell Registry, which listed all the embryonic stem cell lines available for Federal funding. Concerns have been raised regarding the number of viable embryonic stem cells in existence that could be used in Federally funded research.[333]

A number of attempts have been made to amend the Federal legislation on funding, culminating in the Senate introducing the *Stem Cell Research Enhancement Act* in 2006. This Bill was vetoed by President Bush in the same year. The Bill passed through the Senate again, but on 20 June 2007 President Bush vetoed the Bill and issued an executive order, encouraging research into alternative methods of deriving stem cells.[334] Despite the stance by the Federal Government, a number of individual states decided to make funding available for embryonic stem cell research. In 2004, New Jersey became the first state to take this decision and later in the same year California followed suit with the creation of the California Institute of Regenerative Medicine. Since then, Connecticut, Illinois and Maryland have established their own funding initiatives. In addition, Massachusetts, Texas and Wisconsin are interested in establishing public–private funding programmes for stem cell research.[335]

In contrast to the situation in the US, the situation surrounding embryonic stem cell research in Canada is relatively straightforward. Under the *Assisted Human Reproduction Act* (2004), research involving supernumerary IVF embryos is permitted, including the derivation of embryonic stem cells.[336] However, the Act prohibits certain practices, including: the creation of embryos for research or the derivation of embryonic stem cells; reproductive and research cloning; and the creation of chimera and hybrid embryos. The Canadian legislation establishes a strict regulatory framework for the use of embryos in research, to ensure that such research is conducted in an appropriate manner, whether in the public or private sector. The Assisted Human Reproduction Agency of Canada is responsible for implementing and overseeing the legislation and regulations. The *Assisted Human Reproduction Act* (2004) does not apply to embryonic stem cell lines that have already been derived. Guidance on the use of such embryonic stem cell lines is provided by the Canadian Institutes of Health Research.[337]

331 *ibid.*

332 American Association for the Advancement of Science (2007) AAAS *Policy Brief: Stem Cell Research*. Last updated 14 December 2007. Available online at: http://www.aaas.org/spp/cstc/briefs/stemcells/, accessed 18 March 2008.

333 Paarlberg RL (2005) The Great Stem Cell Race. *Foreign Policy* May/June 2007: 44–51.

334 American Association for the Advancement of Science (2007) *op. cit.*

335 Paarlberg (2005) *op. cit.*

336 *Assisted Human Reproduction Act* (2004, c.2). Available online at: http://laws.justice.gc.ca/en/showdoc/cs/A-13.4///en?page=1, accessed 7 December 2007.

337 Canadian Institutes of Health Research (2007) *Updated Guidelines for Human Pluripotent Stem Cell Research*. Ottawa. Available online at: http://www.cihr-irsc.gc.ca/e/34460.html, accessed 7 December 2007.

Elsewhere in the Americas, the majority of countries are generally opposed to research on embryos. Nevertheless, in Brazil, the *Biosafety Law* passed in 2005 allows the derivation of stem cells from supernumerary IVF embryos, provided these embryos have been frozen for at least three years.[338,339] However, both reproductive and research cloning are illegal. In Mexico in 2004, the Government reversed a ban on the use of embryonic stem cells from supernumerary embryos. Following this decision, it is now also possible to create embryos for use in research *via* SCNT.

Legislation/Regulation in Asia-Pacific

In Australia, under the *Research Involving Human Embryos Act* (2002) and the *Prohibition of Human Cloning Act* (2002), it is permitted to conduct research and to derive embryonic stem cells from supernumerary embryos, although reproductive and research cloning are prohibited. In 2006, the *Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act* (2006) was enacted.[340] Under this new Act, the creation of embryos, *via* SCNT, for use in research is permitted, subject to obtaining the necessary licence from the Embryo Research Licensing Committee. All research projects must be approved by a recognised research ethics committee as part of the licence application process, which includes outlining the potential medical and scientific benefits of the proposed research and confirmation that the research could not be conducted without the use of embryos.[341]

Despite this decision at the Federal level, each individual state and territory needs to enact its own legislation for SCNT to be legal at the state level. Victoria became the first Australian state to legalise SCNT in May 2007 and in June 2007 the Lower House of Parliament of New South Wales voted to remove its ban on SCNT.[342]

Elsewhere within the Asia-Pacific region there is increasing interest in and development of stem cell research, which has been fostered and supported by strong Governmental backing.[343,344] For example, in Singapore under the *Human Cloning and Other Prohibited Practices Act* (2004), it is legal to derive embryonic stem cells and to create embryos for research purposes using SCNT. However, embryos created through SCNT must be destroyed after 14 days of development.[345] It should be

338 Nelson L (2005) Biosafety law brings stem-cell research to Brazil. *Nature* 434(7030): 128.

339 International Consortium of Stem Cell Networks (last updated December 2007) *op. cit.*

340 *Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Bill* (2006). Available online at: http://www.comlaw.gov.au/ComLaw/Legislation/Bills1.nsf/0/E58050AC4F8205F6CA257210000725EC/$file/06160b.pdf, accessed 7 December 2007.

341 Australian Government National Health and Medical Research Council (2007) *Ethical guidelines on the use of assisted reproductive technology in clinical practise and research*. Canberra.

342 Pell G (2007) It's all about human life: the real message in the stem cell debate. *The Sydney Morning Herald*, 7 June 2007. Available online at: http://www.smh.com.au/news/science/its-all-about-human-life-the-real-message-in-the-stem-cell-debate/2007/06/07/1181089240429.html, accessed 10 December 2007.

343 Paarlberg (2005) *op. cit.*

344 Isasi RM and Knoppers BM (2006) Mind the Gap: Policy Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries. *Eur J Health Law* 13(1): 9–25.

345 *Human Cloning and Other Prohibited Practises Act* (No.35 of 2004). Available online at: http://www.stemcell.edu.sg/docs/17/Human _ Cloning _ and _ Other _ Prohibited _ Practices _ Act _ 20048.pdf, accessed 7 December 2007.

noted that reproductive cloning and the creation of human-animal hybrid embryos is prohibited. It has been suggested that increased regulation of such research in Asia, allied to increased funding availability, will be beneficial to these countries.[346]

South Korea has also enacted legislation legalising both the derivation of embryonic stem cells from supernumerary IVF embryos and the creation of embryos specifically for research purposes *via* SCNT.[347,348] Similarly to Singapore, South Korea prohibits reproductive cloning. Although the *Bioethics and Biosafety Act* was in place before the controversy surrounding the work of Hwang Woo Suk broke, the research he performed, which was subsequently discredited, was conducted prior to the establishment of the Act. As a result of the revelations surrounding Hwang's research, the *Bioethics and Biosafety Act* is currently being reviewed by the Korean National Bioethics Committee, particularly with regard to permitting further cloning research.[349]

In addition, in both China[350] and India[351] embryonic stem cell research and SCNT are allowed, though it should be noted that in both these countries such practices are regulated through guidelines, as opposed to by legislation.[352,353] In Japan, embryonic stem cell research is authorised under the *Guidelines for Derivation and Utilization of Human Embryonic Stem Cells*.[354] In July 2004, the Expert Panel on Bioethics of the Council for Science and Technology Policy recommended a change in Japanese policy, to allow the creation of human embryos for stem cell research, with limitations, using cloning techniques. Since that time, the Ministry of Education, Culture, Sports, Science and Technology has been working to devise the necessary regulatory framework to implement the report's recommendations.[355]

346 Paarlberg (2005) *op. cit.*

347 See South Korean *Bioethics and Biosafety Act* No. 7150 (2005).

348 Isasi RM and Knoppers BM (2006) *op. cit.*

349 *ibid.*

350 People's Republic of China Ministry of Science and Technology and the Ministry of Health (2003) *Ethical Guiding Principles on Human Embryonic Stem Cell Research*. The authorised translation is available online at: http://www.chinaphs.org/bioethics/regulations _ & _ laws.htm#EGPHECR, accessed 7 December 2007.

351 Director General Indian Council of Medical Research (2006) *National Guidelines For Stem Cell Research And Therapy.* New Delhi. Available online at: http://www.icmr.nic.in/stem _ cell/stem _ cell _ guidelines.pdf, accessed 7 December 2007.

352 International Consortium of Stem Cell Networks (last updated December 2007) *op. cit.*

353 Knowles LP (2004) A regulatory patchwork—human ES cell research oversight. *Nat Biotech* 22(2): 157–163.

354 Ministry of Education, Culture, Sports, Science and Technology – Japanese Government (2001) *The Guidelines for Derivation and Utilization of Human Embryonic Stem Cells*. Tokyo. Available online at: http://www.mext.go.jp/a _ menu/shinkou/seimei/2001/es/020101.pdf, accessed 7 December 2007.

355 Ministry of Education, Culture, Sports, Science and Technology – Japanese Government (2006) *White Paper on Science and Technology, Part 1 Challenges for Building a Future Society—the Role of Science and Technology in an Aging Society with Fewer Children*. Tokyo. Available online at: http://www.mext.go.jp/english/news/2007/03/07022214.htm, accessed on 1 October 2007.

Global Declarations

In recent years, international debates have focused on obtaining consensus on the matter of human reproductive cloning. The United Nations Educational, Scientific, and Cultural Organization (UNESCO) *Universal Declaration on the Human Genome and Human Rights* (1997) forbids human reproductive cloning.[356] Article 11 of the Declaration states that: "practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted." In 2001 an initiative led by France and Germany aimed to deliver a United Nations Convention banning human reproductive cloning. The initiative finally resulted in the *Declaration on Human Cloning*, which was adopted in March 2005 and which declares that, "human cloning is incompatible with human dignity and the protection of human life".[357]

356 United Nations Educational, Scientific and Cultural Organization (1997) *Universal Declaration on the Human Genome and Human Rights*. Available online at: http://portal.unesco.org/shs/en/ev.php-URL _ ID=1881&URL _ DO=DO _ TOPIC&URL _ SECTION=201.html, accessed 7 December 2007.

357 United Nations (2005) *General Assembly Adopts United Nations Declaration on Human Cloning by Vote of 84–34–37.* Press release, published 8 March 2005. Available online at: http://www.un.org/News/Press/docs/2005/ga10333.doc.htm, accessed 7 December 2007.

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Terms of Reference

1. To consider the ethical, scientific and legal issues relating to stem cell research in Ireland.
2. To seek the views of stakeholders and the general public on issues relating to stem cell research.
3. To produce a report detailing all aspects of the Council's deliberations and conclusions on stem cell research.

The Irish Council for Bioethics
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Terms of Reference

1. To identify and interpret the ethical questions raised by biomedicine in order to respond to, and anticipate, questions of substantive concern.

2. To investigate and report on such questions in the interests of promoting public understanding, informed discussion and education.

3. In light of the outcome of its work, to stimulate discussion through conferences, workshops, lectures, published reports and where appropriate to suggest guidelines.

Abbreviations

AHR: assisted human reproduction

ANT: altered nuclear transfer

CAHR: Commission on Assisted Human Reproduction

DNA: deoxyribonucleic acid

EC: European Commission

EGE: European Group on Ethics in Science and New Technologies

EMBO: European Molecular Biology Organisation

EPO: European Patent Office

EU: European Union

FP: Framework Programme (of the EU)

GAEIB: Group of Advisers on the Ethical Implications of Biotechnology

GM: genetically modified

HFEA: Human Fertilisation and Embryology Authority

iPS: induced pluripotent stem cells

IVF: *in vitro* fertilisation

mtDNA: mitochondrial DNA

NBAC: National Bioethics Advisory Commission

NIH: National Institutes of Health (US)

PGD: preimplantation genetic diagnosis

SCNT: somatic cell nuclear transfer

T.D.: Teachta Dála (Member of Irish Parliament)

UK: United Kingdom

UNESCO: United Nations Educational, Scientific, and Cultural Organization

US: United States of America

WARF: Wisconsin Alumni Research Foundation

Legal Instruments and Regulations

National

Australia

Research Involving Human Embryos Act (2002).

Prohibition of Human Cloning Act (2002).

Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act (2006).

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Austria

Reproductive Medicine Act (1992).

Belgium

Law on Research on Embryos In Vitro (2003).

Brazil

Biosafety Law (2005).

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China

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Czech Republic

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Denmark

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Estonia

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Finland

Medical Research Act (488/1999).

France

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Lithuania

Law on Ethics of Biomedical Research (2000).

The Netherlands

Embryos Act (2002).

Norway

Act of 5 December 2003 No. 100 Relating to the Application of Biotechnology in Human Medicine, etc. (The Biotechnology Act).

Portugal

Law (32/2006) Concerning Medically Assisted Reproduction.

South Korea

Bioethics and Biosafety Act No. 7150 (2005).

Singapore

Human Cloning and Other Prohibited Practices Act (No.35 of 2004).

Slovenia

The Law on Treatment of Infertility and Biomedically Assisted Fertilisation (2000).

Spain

Human Assisted Reproduction Techniques Act (2006).

Biomedical Research Act (2007).

Sweden

Act on Measures for Purposes of Research and Treatment using Fertilized Human Ova (1991:115).

The Transplantation Act (1995:831).

The Biobanks in Medical Care Act (2002:297).

The Act concerning the Ethical Review of Research involving Humans (2003:460).

The Genetic Integrity Act (2006:351).

Switzerland

Federal Act on Research on Surplus Embryos and Embryonic Stem Cells (Embryonic Research Act) (2004).

United Kingdom

Human Fertilisation and Embryology Act (1990), Chapter 37.

Human Reproductive Cloning Act (2001), Chapter 23.

Human Fertilisation and Embryology (Research Purposes) Regulations (2001).

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Stem Cell Research Enhancement Act (2006).

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Universal Declaration on the Human Genome and Human Rights (1997).

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Glossary

Note that the terms listed are explained as they apply in the context of the present document. In broader, more general use, some of the terms will have a wider meaning.[358]

Altered Nuclear Transfer: A variation of somatic cell nuclear transfer that limits the cloned embryo's capacity to implant into the lining of the uterus by using genetic modification.

Antigen: A molecule situated on the surface of cells, which is recognised by cells of the immune system and triggers immune reactions.

Autonomy: The capacity to make decisions and take actions that are in line with one's genuine convictions, free from external influences.

Blastocyst: Early embryo consisting of approximately 150 cells; comprised of a cluster of cells called the inner cell mass (from which the organism derives) and an outer layer of cells that form the placenta and other structures necessary for embryonic development.

Blastomere: A cell of the early embryo.

Cell: The basic structural and functional unit of living organisms.

Cell Line: A stable culture of a particular cell type grown *in vitro*.

Cell Replacement Therapy: The treatment of disorders characterised by diseased or damaged cells by transplanting functional cells to reconstitute the tissue/organ.

Chimera: An organism composed of two genetically distinct populations of cells.

Cleavage: Cell division.

Cloning: The process by which a genetic copy of an organism is produced.

Coercion: The practice of compelling a person by use of any form of pressure.

Commercialisation: The consideration and treatment of something or someone as an item that can be bought or sold.

Commodification: The assigning of monetary value to something that traditionally would not be considered in monetary terms, for example, the human embryo.

Cryopreservation: The preservation of cells or organisms by freezing them.

358 Several definitions were sourced from: www.biology-online.org/dictionary/, www.bioethics.gov/reports/white _ paper/glossary.html, and http://stemcells.nih.gov/info/glossary.asp and www.thefreedictionary.com.

Cytoplasm: Area of the cell outside of the nucleus in which most of the cellular work is done and which contains the cell's mitochondria.

Differentiation: The process by which an unspecialised cell becomes a specialised cell with a set function, such as a liver or muscle cell. Dedifferentiation is the reverse process and is also referred to as cellular reprogramming.

DNA: Deoxyribonucleic acid, the biochemical substance that genetic material is made of.

Embryo: Human organism from after fertilisation until the end of the embryonic stage at eight weeks of development, after which the developing human is referred to as a foetus. Embryogenesis refers to the formation and development of the embryo. Embryology is the branch of biology that studies embryogenesis.

Enucleated Cell: A cell that has had its nucleus removed.

Epigenome: Genome wide DNA modifications, other than changes in its sequence, which affect a cell's gene expression.

Fertilisation: The process of union of male sperm and female egg to form the embryo.

Foetus: The developing human, from two months after fertilisation to birth.

Gamete: Reproductive cell. In humans, male and female gametes (sperm and egg, respectively) fuse during fertilisation to produce the zygote.

Gastrula: Early embryo formed during the third week of development. The gastrula undergoes gastrulation, a differentiation process during which the inner cell mass forms three layers that will each provide cells for specific tissue types.

Genome: In general, the genome refers to the whole of an organism's genetic material (DNA) or all of the organism's genes. A gene is a length of DNA that usually contains the information needed to make a protein that will perform a specific function in the cell, giving rise to the particular characteristic associated with the gene.

Germ Cells: Reproductive cells or gametes, *i.e.* egg and sperm cells.

Hybrid (human-animal cytoplasmic hybrid): Embryo created by transferring human DNA by SCNT into an enucleated animal egg.

Implantation: The embedding of the human embryo at the blastocyst stage into the wall of the mother's uterus.

Inner Cell Mass: The cluster of cells of the blastocyst from which the organism develops and from which embryonic stem cells can be isolated. The inner cell mass is also referred to as the embryoblast or embryonic disc.

Instrumentalisation: The treatment of humans as a tool, merely as a means to another person's end.

In Utero: Taking place within the uterus.

In Vitro: Taking place in a controlled environment outside of the body, *i.e.* in the laboratory.

***In Vitro* Fertilisation**: A laboratory procedure in which sperm are placed with an unfertilised egg in a Petri dish to achieve fertilisation. The embryo is then transferred into the uterus to begin a pregnancy or cryopreserved (frozen) for future use.

In Vivo: Taking place inside the body.

Marker: A protein that indicates that the cell producing it has certain properties, *e.g.* stem cell markers allow scientists to determine whether cells are stem cells or not.

Mitochondria: Cellular structures found in the cytoplasm that are responsible for the cell's energy production.

Morula: Early embryo consisting of a solid ball of 16–64 cells.

Multipotent: A cell capable of differentiating into a limited range of cell types producing a variety of cells and tissues.

Nucleus: The part of the cell that contains most of the cell's genetic material, *i.e.* its DNA.

Oocyte: Egg cell.

Ordre Public: Public morality.

Organ: A structure capable of performing a specific function that is essential to the life or well being of the organism, *e.g.* the heart, lungs, *etc.*

Organism: An individual form of life, such as a bacterium, a plant or an animal.

Parthenogenesis: The development of an embryo from an unfertilised egg. The embryo (parthenote) is a clone of the mother.

Patent: A licence provided by a government that confers upon the creator of an invention the sole right to make, use and sell that invention for a set period of time.

Pluripotent: A pluripotent stem cell has the ability to give rise to various types of the cells that develop from the three germ layers from which all the cells of the body arise.

Preimplantation Genetic Diagnosis: Embryo selection technique used during AHR. One cell is removed from the embryo at the eight cell stage and its genetic material is tested.

Proportionality (Principle of): Ethical principle that requires that any harm inflicted be necessary for and carefully balanced against (proportionate to), the good to be achieved.

Protein: Proteins are molecules required for the structure, function and regulation of the body's cells. They are coded for in the DNA of an organism's genome.

Reprogramming: To make a cell with a specialised function, such as a liver cell, dedifferentiate into an unspecialised cell that has the potential to become many cell types.

Sentience: The capacity to react to external stimuli and to feel pleasure and/or pain.

Somatic Cell Nuclear Transfer: A method of cloning that involves transferring the nucleus of a somatic cell into an enucleated egg.

Somatic Cell: A somatic cell is any cell of the body except for sperm and egg cells, which are referred to as germ cells.

Stem Cell: A cell from the embryo, foetus or adult that has the capability to reproduce itself. It can give rise to specialised cells that make up the tissues and organs of the body.

Supernumerary: In excess of the required number or amount.

Telos: An end or goal; ultimate purpose.

Tissue: A group of cells that are characterised by their structure and/or function, such as muscle or nerve tissue.

Totipotent: A stem cell that can give rise to an embryo capable of full development and live birth. These cells can generate all cells and tissues of the body, but also all extra embryonic membranes and tissues necessary to support development and birth.

Xenotransplantation: Transplantation of tissue or organs from one species to another.

Zygote: The cell formed by the fusion of male sperm and female egg during fertilisation.

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