

RECENT DEVELOPMENTS IN STEM CELL RESEARCH:

Social, Ethical and Legal Issues for the Future

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[Editor's Notes: At Corfu 2009, Professor Skene spoke to her recently published paper on this topic, published by the Melbourne Law School of the University of Melbourne, Legal Studies Research Paper, No 385.

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An electronic copy is available at <http://ssrn.com/abstract=1371984>.

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After this paper was published by Professor Skene and delivered at Corfu 2009, in December 2009, 13 new embryonic stem cell lines were approved for research use in the US, with another 96 lines under consideration. The US authorities' approval of the 13 new lines of human embryonic stem cells for scientific research was the first approval since the Obama Administration lifted a ban on their use.

In accordance with the guidelines discussed by Professor Skene, these stem cell lines were derived from embryos that were donated under ethically sound informed consent processes and were made by researchers at Harvard University and Rockefeller University using private funds.

In March 2009, President Barack Obama had lifted restrictions on human embryonic stem cell research imposed by his predecessor, George W. Bush.]

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'While Americans might decide to limit 'halfway' or exotic, science fiction inspired technologies, such as artificial hearts or brain transfers into robot bodies, it would appear unlikely they would ever approve limitations on medical research whose focus is to discover technologies, drugs and scientific techniques which not only maintain qualitative existence but extend life':

Professor George P Smith II.¹

Introduction

In March 2009, President Obama signed an Executive Order reversing President Bush's Order limiting the types of human embryonic stem cells that can receive federal funding for

research. Many people believe this Order signals a new era in this research. However, it is only the first step towards allowing federal funding for American scientists to do the types of embryo research that is allowed in some other countries. Also, science moves at varying speeds and the focus moves quickly from one type of stem cell research to another. At the time of writing, embryonic stem cell research is moving more slowly, due partly to reports of an unregulated stem cell procedure in Moscow causing a young Israeli boy to develop tumors; and partly to new developments in research deriving stem cells without forming embryos. However, embryonic stem cell research may again advance, especially with the increased funds that are expected to become available for it. This paper suggests that if embryonic stem cell research – or any other aspect of stem cell research - ultimately produces effective treatments for human health care, it will receive broad community support, even if there have been earlier reservations about the research that has led to the new treatments.

The paper describes the aims of human stem cell research and the progress that scientists have made over the last few years. It explains how the potential of stem cell treatments has been established in animal experiments and in recent research in which stem cells have been formed from embryos and from body cells; and pluripotent stem cells have been differentiated into other kinds of cells. Some significant experiments have illustrated the effectiveness of stem cell treatment in treating medical conditions, both in animals and humans. In humans, research has been proceeding more slowly but there have been many developments in basic biology and we are on the brink of clinical applications. The US Food and Drug Administration (FDA) has been asked to approve the first drug for human health care produced in the milk of a genetically modified animal and the first US clinical trial of a stem cell treatment in humans, which was about to start when the news of the Moscow procedure was announced, has been placed on hold. The paper considers some of the regulatory issues that have arisen in relation to stem cell research, especially research involving human embryos and human bodily material. It outlines regulatory responses to date, mainly in the US, Canada, the UK and Australia. It examines and evaluates those responses in light of the actual and anticipated progress of the various aspects of stem cells described in the paper and suggests that if research produces safe and effective treatments, that will guide future regulation.

1. Human embryonic and stem cell research: aims, achievements and future prospects

1.1 Aims of research

One aim of human stem cell research is to treat patients by transplanting healthy cells derived from their own bodies to stimulate the repair of diseased tissue. The concept of treating patients in this way has been established for more than 40 years in treatment for leukemia. Bone marrow (a type of body tissue containing stem cells) is obtained from donors and transplanted into patients. If the transplanted cells come from the patient, rather than a donor, the cells will not be rejected as foreign material by the patient's immune system and the patient will avoid a life-time of immuno-suppressive drugs which

may have adverse effects. Conditions that might be treated like this include spinal cord injury and 'stroke, burns, heart disease, diabetes, osteoarthritis, rheumatoid arthritis, vision disorders, motor neuron disease and liver diseases ... , Parkinson's and Alzheimer's diseases'.² Many of these diseases are caused by the deterioration of the body and they increase with a patient's age, an important factor with an ageing population in many countries.³ For patients with diseased organs, it is hoped that instead of having organ transplants, the injection of healthy cells will make their diseased organs regenerate themselves. Other research aims to 'turn off' the stem cells that cause some cancers.⁴

Stem cells are also valuable when scientists are studying diseases. They provide a means for scientists to create a 'disease in a dish'. For example, scientists will be able to take skin cells from patients with a condition like motor neuron disease, turn them into stem cells in a test tube and then stimulate those cells to produce nerve cells. They will then have nerve cells with the characteristics of motor neuron disease to study the development of disease and to test new drugs.

1.2 Embryonic stem cells and stem cells derived from body cells

Human stem cells may be obtained from human embryos or from body cells. The latter are often called 'adult' stem cells but they could also come from a child. Embryonic stem cells are pluripotent – they can develop into any other type of cell in the body. Until recently, stem cells derived from body cells could form only one type of body part or tissue, or a small sub-set of it, according to where they came from. Bone marrow stem cells, for example, could produce only bone marrow and the white blood cells produced by bone marrow cells. They could not be transformed into heart or liver cells and, to date, the main field in which stem cell treatment has been effective in human patients is the transplant of donated bone marrow cells to treat patients with leukaemia. That has been possible because it is not necessary to change the donated bone marrow cells into another kind of cell to provide the treatment. However, that treatment works only to treat blood disease. It cannot be used to repair damaged spinal tissue in paraplegic patients, or to treat diabetes, which affects pancreatic tissue. Also, as noted earlier, patients who receive donated bone marrow need life-long immuno-suppressive drugs to prevent rejection of the transplanted tissue.

In recent developments in stem cell research, Japanese scientists 'reprogrammed' body cells by introducing (via genetically modified retroviruses) four transcription factor genes essential for pluripotency in ES cells.⁵ The number of transcription factors has since been reduced and, in a later report, Hans Schöler of the Max Planck Institute for Molecular Biomedicine reportedly used only one transcription factor to reprogram mouse adult neural stem cells.⁶ That process 'still involve[d] viruses that permanently modify the cells' DNA, which precludes using the cells in any potential clinical applications';⁷ but in the latest research, scientists have reported deriving stem cells from body cells without viruses or other factors affecting the ongoing genetic constitution of the cells.⁸ These studies effectively turned back the biological clock of the body cells giving them the core characteristics of embryonic stem cells. These induced pluripotent stem (IPS) cells can

then be 'differentiated' into all other tissue types. Professor Doug Melton (from Harvard) also recently established that it is possible to turn one type of body cell into a different type of body cell (cellular reprogramming) without doing the reversion step and going through pluripotency.⁹

Some people have said that this work will replace embryonic stem cell research but that is arguable (as suggested later in the paper) and many scientists believe that both types of research should continue for the present. One of the main challenges in stem cell research, both with embryonic stem cells and stem cells derived from body cells, is to differentiate the pluripotent stem cells into the other kinds of cells needed to replace diseased tissue (this may also include human sperm and eggs).¹⁰

Differentiating pluripotent stem cells when stem cells are derived from body cells is a particular challenge as they are less adaptable than embryonic stem cells. One reason for studying human embryonic stem cells is to understand how these stem cells develop into other types of cells: how does an embryo form into all the other tissues of the human body? That information will help scientists trying to differentiate stem cells into particular cells of interest.

1.3 Achievements to date

In humans, much of the progress to date in stem cell research has been in pure biology – understanding the development of early embryos and how they differentiate from pluripotent cells into specialized cells, like nerve cells, cardiac cells and muscle cells. However, there has been significant progress in research on animals and, very recently, even in human patients, including the following developments in key areas.

Derivation of embryonic stem (ES) cells and induced pluripotent stem (IPS) cells.

Mouse ES cells were first cultivated at the universities of Cambridge and California in 1981; primate ES cells, by researchers in Wisconsin in 1995; and human ES cells, again by researchers in Wisconsin, in 1998; and in 2009 in China.¹¹ The first published human ES cell line was created in Wisconsin in 1998.¹² The first ES cells derived from a hybrid (fused human cells and rabbit eggs, discussed later in the paper) were obtained by Hui Chen in China in 2003.¹³ Groups in the US and the UK have succeeded in cloning human embryos and American scientist Robert Lanza recently said that 'fully human cloned embryos' are likely to be a better source of ES cells than interspecies embryos.¹⁴ No one has yet produced stem cells from a cloned human embryo.¹⁵ In 2006, Shinya Yamanaka of Kyoto University converted adult mouse cells into IPS cells and has since derived IPS cells from human skin cells.¹⁶ At the same time, Thompson and Junying Yu at the University of Wisconsin obtained IPS cells by exposing a patient's skin cells to four transcription factor proteins that turned specific genes on and off triggering the skin cells to behave like ES cells.¹⁷ In 2009, Australian scientists also derived IPS cells.¹⁸

Differentiation of ES cells. Scientists at the Monash Institute of Medical Research reported in 2002 that they had differentiated mouse ES cells into nerve cells. Since then,

mouse and human ES cells have been differentiated into endodermal cells (the precursors of pancreatic cells) and insulin-producing cells.¹⁹ Human ES cells have also been differentiated into neural precursor cells, cardiomyocytes and haematopoietic (blood forming) precursor cells.²⁰

Differentiation of IPS cells; cellular reprogramming. A technique to achieve 'de-differentiation' was demonstrated in specific patients by scientists at Harvard and Columbia universities in July 2008. They reportedly 'created the first personalized stem cells for patients with a genetic disease by rewinding their skin cells to an embryonic state'.²¹ To achieve this, scientists removed 3-millimeter patches of skin from the arm of an 82-year-old woman and her 89-year-old sister, who share a rare genetic mutation that causes about 2% of Amyotrophic Lateral Sclerosis (ALS) cases. They then isolated fibroblast cells from the sisters' skin biopsies and infected them with viruses, prompting the cells to express four dormant genes - Klf4, Sox2, Oct4 and c-Myc - that are active during early embryonic development.²² This procedure resulted in the production of eight stable disease-specific stem cell lines to study in the laboratory – which had not been possible before. As one co-author of the paper on this research reportedly said, 'There's no way we could go to an ALS patient and take a sample of their motor neurons [which reside in the brain]'.²³ Only one week after the ALS disease-specific stem cells were made, George Q. Daley from Harvard Stem Cell Institute (HSCI) and HSCI colleagues Konrad Hochedlinger and Chad Cowan produced disease-specific stem cell lines from patients with ten medical conditions - Duchenne muscular dystrophy, Becker muscular dystrophy, juvenile-onset (type 1) diabetes, Parkinson's disease, Huntington's disease, Down syndrome, ADA severe combined immunodeficiency, Shwachman-Bodian-Diamond syndrome, Gaucher disease, and a carrier of Lesch-Nyhan Syndrome.²⁴ By watching the disease-specific stem cells differentiate in the lab, scientists can observe how these debilitating diseases take hold and progress at a cellular level, which it is impossible to observe in a living patient.²⁵ Similarly, in 2008, skin cells from a patient with a genetic disease called spinal muscular atrophy were reprogrammed into stem cells that could be used as a model of the disease.²⁶

At that time, it was thought that an adult IPS cell would have to be taken back in time to the pluripotent stage, like an ES cell, before it could be reprogrammed into another kind of cell, usually a therapeutically important cell type for tissue regeneration. However, later in 2008, Doug Melton from Harvard University reported that he had been able to 'short-circuit' the process of re-programming an adult cell into a differentiated cell of another kind in mice through a process he termed 'lineage reprogramming'.²⁷ Using a strategy of re-expressing key developmental regulators *in vivo*, Melton's team was able to identify three transcription factors that together reprogrammed differentiated pancreatic exocrine cells in adult mice into cells that closely resemble beta-cells.²⁸ Despite this success, it is still

unclear whether distantly related cell types can be fully converted with a lineage reprogramming approach.²⁹

In other recent research, a team of German scientists succeeded in generating pluripotent stem cells from tissue biopsied from human testicles. It was found in this study that germline stem cells (GSCs) have all the same capabilities of pluripotent stem cells as they differentiated into various types of somatic cells from all three germ layers when grown under conditions used to induce the differentiation of human ES cells. It has been suggested that this success shows that human adult GSCs can provide easy and non-controversial access to individual cell-based therapy without the ethical and immunological problems associated with human embryonic stem cells.³⁰ Japanese scientist Hiromitsu Nakauchi has reportedly turned human stem cells into platelets which encourage blood clotting and reduce excessive bleeding.³¹

ES cell 'treatment' in animals. Scientists funded by the US National Institutes of Health (NIH) who were studying the loss of neurons in the brain after a stroke have described how manipulated ES cells can be used to generate neurons to replace those lost by disease. Scientists can already drive human ES cells into becoming neurons outside the body. However, transplants of these cells into animal models of human diseases sometimes 'overgrow' and form tumors, suggesting that the transplants contain both desirable neurons and undesirable undifferentiated cells. Scientists now claim they have developed a cell culturing method that selects only human neural stem cells (hNSCs), and then drives them to become mature neurons, with no undifferentiated cells remaining. Transplants of these cells into rats did not produce any tumors, at least within the two-month period of observation. In addition, rats that had suffered a stroke regained the use of their damaged paws. In another study³², mouse ES cells transplanted into rats with impaired hearts differentiated into normal myocardial cells that remained viable in the rat's heart for more than four months.³³ In 2008, scientists at the Memorial Sloan-Kettering Cancer Centre in New York, led by Lorenz Studer, reported in *Nature Medicine* that they had treated mice that had been bred to have a condition like Parkinson's disease, with cloned embryonic stem cells. They created 187 lines of cloned embryonic stem cells from 24 mice with the condition by inserting DNA from the mice into an enucleated egg (somatic cell nuclear transfer, or the 'Dolly technique'), and cultured them in the laboratory to grow into nerve cells that produce dopamine. They then injected those cells into the mice's brains, so that each received neurons grown from their own cloned stem cells. Their symptoms improved and they showed no signs of rejecting the transplanted material.³⁴ At Kyoto University, Jun Takahashi's group are pursuing clinical treatment of a monkey model of Parkinson's disease with neuronal precursor cells derived from ES and IPS cells. Treatment with the ES symptoms in the affected monkeys without rejection over a 14-week period.³⁵

IPS cell 'treatment' in animals. Rudolf Jaenisch's research group at Massachusetts Institute of Technology (MIT) have made some significant advances in this area of treatment in relation to mice. His group successfully reprogrammed cells from mouse tails

into IPS cells that then differentiated into cells that produced healthy red blood cells to successfully treat mice suffering from a humanized version of sickle cell anaemia.³⁶ This experiment was the first proof in principle of the therapeutic use of IPS cells.^{37 38} In 2008, his laboratory also reported that neurons derived from IPS cells successfully integrated into fetal mouse brains and reduced symptoms in a Parkinson's disease rat model.

Adult stem cell 'treatment' in animals. Stem cells have also been taken from animals' bodies and used directly in 'treatments' without being made pluripotent through the IPS process. In January 2008, scientists observed an improvement in a mouse model of muscular dystrophy (MD) treated with muscle cells derived from mouse ES cells.³⁹ Following on this research, US NIH-funded scientists were able to isolate a specific type of adult mouse muscle stem cell that improves muscle function when transplanted into mice suffering from muscular dystrophy. This method involved the transplantation of mouse muscle stem cells (already differentiated) which were surprisingly able to establish themselves for continued repair and replacement of the damaged muscle.⁴⁰

A British neuroscientist, Geoffrey Raisman, grafted stem cells from a rat's nose into a lesion in its nervous system that prevented it moving its left paw. Not only did the cells survive the transplant, they triggered the growth of severed nerve fibres, which resulted in the rat being able to move its left paw again. Raisman and his team have identified that adult nerve⁴¹ fibres in the nasal cavity continually renew themselves, so when transplanted somewhere else, they continue this renewal with the ability to grow across the gap in the nerve pathway and restore function. Scientists hope to identify a similar human adult muscle stem cell population in order to learn more about what enables the cells to self-renew and possibly to learn to boost their regenerative potential. This research may one day lead to treatments for individuals with MD.

Cheryl Adams, a pioneer in veterinary stem cell therapy in Illinois, has treated 30 dogs for different joint and bone problems with stem cells derived from their own adult body tissue with exceptional results... For example, an 8-year-old German Shepherd had developed osteoarthritis and hip dysplasia. After removing some fat from the dog's abdomen, Dr Adams isolated the stem cells from this fat and injected the stem cells into the dog's joints. The results from this \$3,000 procedure were 'spectacular and almost immediate', according to Dr Adams⁴².

Stem cell 'treatment' in humans. Internet searches report stem cell treatments for humans that have apparently had some success.⁴³ A paralyzed man with a broken spinal cord was reported to be walking again after his stem cells (derived from his own bone marrow) were injected into the site of paralysis.⁴⁴ Similar success stories are reported on the Nichi-In Centre for Regenerative Medicine website.⁴⁵ However, to date these treatments have not been validated in clinical trials. The International Society for Stem Cell Research (ISSCR) is concerned about the safety of these procedures which are offered without proper scientific evaluation to vulnerable patients, and the risk of maverick practitioners in an area of rapidly developing technology;^{46 47} a risk that proved well

founded after later 'descriptions of an unregulated transplant of fetal neural stem cells [in Moscow] that developed into tumours in a patient's brain and spinal cord'.

Formal clinical trials have recently started to test stem cell treatments in human subjects. Seventeen patients (of a test group of 21) who were suffering from the early stages of multiple sclerosis reportedly showed "significant improvement in their condition" after being injected with stem cells from their own bone marrow by doctors in Chicago; and a 'control trial ... has been approved with 110 patients and research teams in the United States, Canada and Brazil'.⁴⁸

In Miami, a study of 45 patients with heart disease is currently under way and the first patient has reportedly been injected with stem cells extracted from his bone marrow. The cells were injected during a triple bypass operation and the patient will be observed to see if new tissue is generated in the heart and the heart is pumping more effectively.⁴⁹

Other trials involve patients with spinal injuries. The first clinical trial of ES cell therapy for acute spinal cord injury has been planned by the pharmaceutical company Geron,⁵⁰ whose researchers apparently plan to test their human ES stem cell-derived drug (GRNOPC1) in patients with spinal cord injuries. The hES cells they used to create GRNOPC1 were derived from fertilized embryos unused in IVF procedures. Researchers hope that the ES cells will differentiate into oligodendroglial progenitor cells and establish themselves in spinal cord patients without rejection. Preliminary tests conducted by Geron reportedly show that the ES cells evade direct attack by the human immune system, so that patients treated in this way would require significantly lower doses and/or shorter courses of immunosuppression than those required for patients who undergo solid organ transplants.⁵¹ Geron submitted a 22,500-page investigational new-drug application to the Food and Drugs Administration (FDA) and the trial has been approved. It was initially due to start in 2008 but it was deferred because of safety concerns. It was then reportedly set to proceed in 2009. Currently, however, it has been placed on 'clinical hold' after 'descriptions of an unregulated transplant of fetal neural stem cells [in Moscow] that developed into tumours in a patient's brain and spinal cord'.^{52 53} Other clinical trials are planned by another US company, Neural Cell, which has recently applied to the FDA for approval, according to the President of Neural Cell, Richard Garr.

Patients disabled by stroke will reportedly be recruited into a Phase I clinical trial in Glasgow later this year, in a project to be undertaken by ReNeuron Group Plc, which was approved by the UK Medicines and Healthcare Products Regulatory Agency in January 2009. A total of 12 patients will receive ReNeuron's ReN001 cell therapy derived from fetal stem cells, administered between six and 24 months after their stroke.⁵⁴

In other clinical developments, the US FDA has been asked to approve the first drug for human health care produced by a transgenic animal (the protein-based blood-thinning drug known as as ATryn will be produced in the glands of transgenic goats and harvested in their milk).⁵⁵

2. Regulatory issues and responses

2.1 Activities permitted by law subject to regulatory controls and ethical oversight *In vitro stem cell research; research on animals.*

The first experiments in stem cell research were conducted *in vitro* or on animals. There was discussion about the potential risks and ethical implications of 'interfering' with the genetic constitution of organisms and transferring genetic material from one organism to another. There were also concerns expressed about research on animals. These issues have now been largely resolved and the research is generally permitted by law, subject to ethical oversight. They will not be discussed more fully in this paper.

Use in research of 'spare' human embryos (donated by couples in fertility programs). The use of human embryos donated by couples undergoing fertility treatment in research is accepted in the UK, Canada,⁵⁶ Australia,⁵⁷ and many other countries, most recently the US. The British Fertility Society states that it supports research on so-called 'spare' human embryos very strongly on the basis that these embryos would be discarded in any case, and the benefit to society from such research strongly outweighs ethical and moral concerns about the status of the embryo.⁵⁸ To the best of its knowledge, none of its members objects to research on spare human embryos.⁵⁹

In the US, research on spare human embryos has not been prohibited by federal law but, until March 2009 when President Obama signed the Executive Order allowing federal funding for this research, research on ES cells could be done with federal funding only on the genetically diverse ES lines derived on or before August 9, 2001,⁶⁰ and only 'about 20 "presidential lines" are still viable'.⁶¹ Federal funding in the US for stem cell research was restricted to \$90 million from 2001-2005 by the Bush Administration and was cut altogether in 2005 when President Bush took an extremist stance on the subject by freezing all federal funds for any further research.⁶² Individual States did have authority to pass laws to permit human ES cell research on ES cell lines that were not eligible for Federal funding and some did – California, Michigan and Missouri.⁶³

However, as a result of these obvious limitations, the Stem Cell Research Enhancement Act was passed by Congress in 2007. It amended the Public Health Service Act to state that regardless of the date on which stem cells were derived from a human embryo, the Secretary of Health and Human Services shall conduct and support embryonic stem cell research.⁶⁴ It also set out various ethical guidelines which ultimately aimed to promote safe stem cell research. President Obama was a propagator of the Stem Cell Research Enhancement Act 2007, on behalf of the Democrats, and he emphasized that by expanding scientific access to ES cells which would be otherwise discarded, the Act would help scientists and researchers to develop treatments and cures to help people who suffer from illnesses and injuries for which there are currently no cures.⁶⁵ Soon after its enactment, President Bush vetoed the Act on moral and ethical grounds. There has also been ongoing opposition to embryo research in some states.⁶⁶

During the Bush administration, embryo research had to be done completely separately from any activities that were financed by federal funding. This funding issue 'stymied research in the US according to Professor Christine Mummery, a Professor of Developmental Biology at Leiden University Medical Center in The Netherlands. She reportedly said:

What's happened in the U.S. is that people have become very frustrated and a lot of private initiatives - like the Harvard Stem Cell Institute - were started up to circumvent the lack of National Institutes of Health (NIH) funding. NIH researchers are either left behind or have a huge administrative burden. You go into a lab in the States and they say; 'this is our NIH lab, and this is our other lab'. They have to buy one microscope to look at NIH lines and another to look at other lines. They have to administer all the stem cells separately. There are even dotted lines in a lab which you can and cannot cross.⁶⁷

In March 2009, President Obama signed an Executive Order reversing President Bush's Order limiting the types of human embryonic stem cell research that can receive federal tax dollars.⁶⁸ He indicated his intention to refer the issue to Congress to change the policy,⁶⁹ which would meet the continuing concerns of some scientists who believe that 'research policy is better set by a comprehensive law than by a revocable directive'.⁷⁰ New legislation could also repeal the 14-year-old 'Dickey-Wicker Amendment', banning the use of federal money for research that creates or destroys human embryos.⁷¹ This would not only make it clear that scientists can lawfully use embryos donated from fertility treatment programs in federal funded research. It would also be possible for them to create embryos specifically for research with federal funding.

It might be thought that there will be less demand to do embryonic stem cell research now that pluripotent human stem cells have been derived from IPS cells. There are likely to be fewer religious and ethical objections to IPS cell research⁷² and some leading scientists in the field, such as Ian Wilmut, the creator of Dolly the sheep, have reportedly said that they will undertake only "adult" stem cell research in the future.⁷³

On the other hand, as discussed earlier, there are reasons to continue research on human embryonic stem cells. They are more adaptable than stem cells derived from body cells and they reproduce indefinitely. Also, research on early embryos is necessary to understand how pluripotent cells develop and differentiate into other kinds of cells. One of the scientists doing the recent ground-breaking research on deriving matched neurons from the skin cells of patients with Lou Gehrig's disease reportedly described embryonic research as the 'gold standard' for stem cell research, which is limited by the ban on paying women for their eggs.⁷⁴ Other scientists have acknowledged that their research on IPS cells has been assisted by earlier research on embryos.^{75 76} In time, hES cells may provide the best opportunities for clinical treatment. The Geron trial, recently approved by the FDA, would have been the first using ES cells but, at present, that trial has been deferred⁷⁷.

The future of treatments developed from hIPS cells is also uncertain. It has been said that the genes used to reprogram adult cells are, themselves, associated with cancer, so iPS cells made in this way will not be used clinically.⁷⁸ Even if the IPS cells can be derived without using a cancer-inducing protein, they may still present clinical problems. Eric Forsberg, Director of the WiCell Research Institute, reportedly said:

*... reprogramming of adult cells is extremely inefficient and incomplete. The genome clock is not completely reset and this likely plays a role in the health problems that cloned animals have - Dolly the sheep had arthritis and was euthanized due to a progressive lung disease. This raises the possibility that tissues developed from reprogrammed iPS cells might not function normally.*⁷⁹

According to the same report, Forsberg also pointed out that:

*the extent to which a person's genome is reset can vary from person to person, and this could mean that each person will require an individualized reprogramming regimen in order to create iPS cells for therapeutic use. However, it is unlikely that the FDA would approve such an individualized protocol because the agency likes strict uniformity and conformity in therapeutic protocols, not different protocols for different people.*⁸⁰

Christine Mummery reportedly said that: 'It could save a lot of time and effort of taking the wrong drugs through. Or it may allow drugs through which are lost at an early stage, because they affect the animal cells but don't have an effect on human cells. It may also allow more and better drugs to come through the first tests or flag up safety issues at an earlier stage'.⁸¹ She also said that using human embryonic stem cells in testing drugs could end animal testing.⁸²

Nevertheless, the early clinical trials of stem cell treatments inevitably involve risks for the participants. Ethicist Ruth Faden said, regarding the Geron trial, that it would be the first time that a product of human embryos has been introduced into a person; if it causes problems, such as the formation of tumors, it would not be possible to retrieve the inserted material; and it may be difficult to obtain a voluntary, informed consent from patients who have suddenly become paralyzed after a devastating injury.⁸³ However, there are protective measures for patients in the law and procedures for ethical oversight: FDA approval; review by hospital ethics committees (institutional review boards); the established principles of informed consent (voluntary decision without coercion; proper disclosure of risks including that risks are not known; assessment of patient's understanding of information provided; ability to withdraw at any time without detriment to treatment; and reporting of adverse effects to a Data Safety Monitoring Board which may stop the trial).⁸⁴

Use in research of human embryos created specifically for research (particularly by somatic cell nuclear transfer (SCNT) or therapeutic cloning). Creating human embryos

specifically for research is more problematic than using donated embryos for research. Embryos donated from fertility programs were created initially for the purpose of having a child and, if they are not needed for that purpose, and they are not donated for research, they will generally be destroyed. In contrast, creating a human embryo, in the knowledge that it will be destroyed, is more morally questionable.⁸⁵

In the UK, it is lawful to create a human embryo for research by fertilizing a human egg with human sperm.⁸⁶

In Australia, it is lawful to do research on human embryos only if they are created by somatic cell nuclear transfer (SCNT), that is, not by fertilizing a human egg by human sperm.⁸⁷

In both countries, the research may be done only under license; the resultant embryos may be used only for research, including the extraction of stem cells; and the embryos must be destroyed within 14 days. In the US, there is no federal law on the creation of embryos by SCNT but federal funding is not permitted for this research. It has been done by a private company. On Sunday, November 25, 2001, Advanced Cell Technology, a biotech Company in Worcester, Massachusetts, announced the first successful cloning of a human embryo. The Executive Order recently signed by President Obama allows federal funding for research on human stem cells derived from donated embryos, but not for research involving the creation of embryos of for research.

Considering the future, one may question the ethical basis of the distinction between 'SCNT embryos' and 'sperm-egg embryos'.⁸⁸ If eggs are donated for research and sperm is donated for research, why should a researcher not be permitted to fertilize the eggs for research, subject to obtaining a license and complying with other statutory requirements? Also, generating human embryos for research may be better than using donated embryos, both from a scientific and ethical perspective. Cells obtained from these embryos would not have been frozen and donors of the sperm and eggs would know in advance that the embryos would be created to be used for research.⁸⁹

2.2 Activities widely condemned or prohibited and likely to remain prohibited

At the other end of the spectrum, some activities within the realm of human embryonic or stem cell research arouse such concern that they are the subject of international instruments to which many countries subscribe and they are expressly prohibited by legislation in many jurisdictions. Activities in this category include the development of a human embryo for more than 14 days; the implantation of a human-animal embryo or an embryo that has been used in research in a woman's body; and implanting a human embryo in an animal or vice versa. For these activities, the law sets limits for scientists concerning research that is generally accepted and legally permitted and research that must not be attempted. This approach may reassure the community that the activities about which people are most concerned will not be permitted and will attract the most

stringent penalties available to the law.⁹⁰ I have heard of no scientists who want to do these things⁹¹ and it is difficult to imagine why they would.

2.3 Activities that are currently widely condemned or prohibited but on which opinions are divided, or may change

However, even for activities that have aroused particular concern, views sometimes differ concerning what should be allowed. There are differences on some issues between countries. Also, opinions sometimes change as knowledge expands and activities that were once condemned may be viewed differently in at least some of their applications.

Human reproductive cloning. Human reproductive cloning (cloning to breed identical people) is commonly considered an activity of such concern that it should always be banned, either on moral grounds or to protect the welfare of the child to be born. Concern has been so universal that an international instrument condemning it, the *UNESCO Declaration on the Human Genome and Human Rights*, 1997 was approved by 186 nations. Article 11 of the Declaration states that: 'practices such as reproductive cloning of human beings shall not be permitted' and many countries have legislated to ban this practice in their own jurisdiction. Human reproductive cloning is specifically banned in many countries including the UK,⁹² Canada,⁹³ Australia⁹⁴ and many European countries.⁹⁵

In the US, there are currently no federal laws that ban human cloning and a number of federal bills to introduce a ban have failed to pass.⁹⁶ However, current US federal regulations prohibit federal funding for research into human cloning. This effectively prevents such research from occurring in public institutions and private institutions such as universities which receive federal funding. Some American states ban reproductive cloning and some also ban therapeutic cloning (somatic cell nuclear transfer (SCNT)).⁹⁷ In Indiana, for example, both reproductive and therapeutic cloning are banned; public funds may not be used for cloning; and a hospital's license may be revoked if its employees undertake human cloning.⁹⁸

In California, on the other hand, reproductive cloning is banned but cloning for research is permitted;⁹⁹ and in Missouri, reproductive cloning is banned only if it seeks to develop embryos into a newborn child and uses state funds. California, New Jersey and Massachusetts are the only states to explicitly endorse embryonic stem cell research and somatic cell nuclear transfer and the Acts of California, New Jersey and Connecticut provide funds for embryonic stem-cell research (the Massachusetts Act does not provide for any financial support as that state no doubt relies on its reputation to attract private investment).¹⁰⁰

However, despite continuing concern about the possibility that genetic technology might be used to enable a child to be born whose genes are almost the same as those of the person whose body cell was used to create the embryo,¹⁰¹ some people have questioned the need always to prohibit reproductive cloning. If it could be established that the procedure is safe for the child to be born from it, then the ethical objections might be

challenged. This form of technology could enable a person who is infertile to have a child who is genetically related to that person, which would not otherwise be possible. It may be objectionable to deliberately breed identical people, the scenario of the film *Boys from Brazil*. But is it wrong for people to try to have a child who shares their genes?

Deriving human gametes from human skin cells. The same argument might be made about new research that might enable an infertile person to have a child by producing gametes (sperm or ova) from his or her own body cells through IPS.¹⁰² Scientists have already taken the first step towards this procedure. As explained earlier, human IPS cells have been derived from human skin cells by transferring selected genes to cells to activate their development (Professor Shinya Yamanaka's technique);¹⁰³ and, in the most recent research on patients with Lou Gehrig's disease, scientists have differentiated human stem cells obtained from skin cells into neurons matched to the patients.¹⁰⁴ In time, it may be possible to convert stem cells derived from skin cells (and stem cells derived from embryos) into sperm or eggs.¹⁰⁵

The Hinxton Group, an International Consortium on Stem Cells, Ethics and Law, recently issued a Consensus Statement concerning research that may lead to human sperm and eggs being derived from stem cells which could come from embryos or from body cells.¹⁰⁶

Some progress has already been made in research on mice, in which sperm-like cells and egg-like cells (the beginnings of sperm and eggs) have been derived from skin cells but they have not developed to mature sperm and eggs. However, some of the early sperm-like cells appear to have matured when inserted into the testis of a mouse and have led to the birth of live pups, though they had deformities and died within months.¹⁰⁷

Sale of Human Sperm, Eggs and Embryos. If human embryo research is to continue, either in place of human-animal embryo research or in addition to it, large numbers of human eggs will be needed¹⁰⁸ and there is a shortage of human eggs for use in research. This raises the issue whether monetary payments or other inducements should be permitted for donating human eggs and embryos for use in research. In the UK, Canada and Australia, the tradition in medical research has been that all tissue used in research should be given gratuitously, including human eggs and embryos; and there payments are not permitted beyond reasonable expenses,¹⁰⁹ such as reimbursement of the donors' medical expenses and compensation for loss of earnings due to the donation. Similarly, European countries disapprove of commercialization or obtaining financial gains from the donation of human reproductive materials. In the US, there is no federal legislation governing the sale of human eggs and they may be sold for a 'fair price' for use in fertility programs.¹¹⁰ The meaning of 'reasonable expense' and 'a fair price' is open to interpretation.¹¹¹ What type of monetary payment is appropriate (e.g., cash or in-kind services, such as being advanced in the waiting list for fertility treatment)?¹¹²

In 2000, the Ethics Committee of the American Society of Reproductive Medicine (ASRM) stated (in the context of egg donation to assist infertile couples to have children) that:

Payments to women providing oocytes [eggs] should be fair and [yet] not so substantial that they become undue inducements that will lead a donor to discount risks.¹¹³ Although there is no consensus on the precise payment that oocyte donors should receive, at this time sums of \$5,000 or more require justification and sums above \$10,000 go beyond what is appropriate.¹¹⁴ Programs recruiting oocyte donors and those assisting couples who have recruited their own donors should establish a level of compensation that minimizes the possibility of undue inducement of donors and the suggestions that payment is for the oocytes themselves.¹¹⁵

Additionally, the Committee stated that, to avoid commodifying human gametes, compensation should not be based on a donor's ethnic or personal characteristics. The ASRM Ethics Committee recommendation serves as compensation guidelines for the Society for Assisted Reproductive Technology's (SART) clinical practices.¹¹⁶

Similar principles would seem appropriate where eggs are donated for research, especially where the woman must undergo ovarian stimulation and surgical egg collection for the research alone, rather than eggs that have been formed for fertility treatment but are no longer needed. But if the payment or inducement is not so great as to threaten the woman's ability to provide free and voluntary informed consent for donation;¹¹⁷ or to appreciate the risks of the procedure;¹¹⁸ or to agree to the procedure only because of the inducement, then one might question why women should be prevented for donating their eggs for research. If there is concern that eggs may be imported for research from other countries that have less stringent protection for donors, then legislation could be passed to prohibit the importation of gametes and stem cell lines that have not been procured in accordance with the local laws governing monetary payments and consent.

However, even if human eggs could be sold, it is unlikely that there would be a large number available for research. Many human eggs will be needed and women who may wish to be donors will no doubt be deterred when they are told about the risks of donation. After gaining approval from various regulatory boards at Harvard University last year, Kevin Eggan and his collaborators began recruiting egg donors with advertisements in local papers and disease-advocacy magazines. Eggan said 'We've had hundreds of calls from women who are interested in donating, but when they find out about the time, effort, and pain involved, they simply can't take the time to go forward'.¹¹⁹ Eggan blames the dearth of donors on Massachusetts regulations that prohibit researchers from paying women for their eggs. The law is meant to prevent coercion of poor women who might undergo the procedure out of financial need. But women who undergo the same procedure to donate eggs for assisted reproductive technology (ART), in which infertile women use another woman's eggs to get pregnant, receive payments from \$3,000 to \$10,000. 'If we feel comfortable compensating women who donate eggs for ART - and infertility is a terrible disease - why aren't we comfortable compensating women for donations that could aid other serious diseases?' Eggan asks.¹²⁰ But even if attractive compensation is provided, the number of eggs obtained is likely to remain relatively small.

Creating human-animal embryos. The creation of human-animal embryos is banned in Australia,¹²¹ in Canada¹²² and in many European and other countries. It is not currently banned in the US (the Human-Animal Hybrid Prohibition Bill was introduced in 2008 but has not been passed); but federal funding is not permitted for this research in the US.

In the UK, on the other hand, the first human-animal embryo was created in 2008 by scientists at Newcastle University under a license from the Human Fertilization and Embryology Authority (HFEA).¹²³ The validity of that license was confirmed in 2008 when the Human Fertilization and Embryology Act 1990 was amended by Parliament.¹²⁴ Since then, two more licenses have been granted and the first human-animal embryo has been formed, though no stem cells have yet been derived from it. The Act covers what are called 'human admixed embryos'. These include not only cybrids (or cytoplasmic hybrids) which are formed by 'incubating' human genetic material in cytoplasm from an animal and would be almost entirely human, but also other embryos that are up to half 'animal'.¹²⁵ Researchers are required to obtain a license from the HFEA before creating hybrid embryos and must destroy them after 14 days.

If stem cells that are almost entirely human can be produced from human-animal embryos, then that could provide an advantage for scientists undertaking stem cell research.¹²⁶ Although these stem cells could not be used in treatment, the scientists could derive large numbers of these stem cells for research, including stem cells that carry the genes for particular diseases, without the need to use donated human eggs. If the research on these stem cells yields interesting results, one can imagine pressure mounting to lift the ban on creating human-animal embryos for research. This happened in a limited and slightly different context in Australia, when an exception was provided to the general ban on creating human-animal embryos, to allow the so-called 'hamster test' to be performed.¹²⁷ This involves fertilizing a hamster egg with human sperm to test the viability of that sperm. If a hamster egg could not be used, it would be necessary to use a human egg and those eggs are in short supply.

Similarly, in the US, Britain and some European and other countries, the law allows the breeding of animals with human genes to produce drugs for human health care. The most recent example, as mentioned earlier in the paper, is the protein-based blood-thinning drug known as ATryn that will be produced in the glands of transgenic goats and harvested in their milk. This drug will be evaluated by the Food and Drugs Administration – the first time it has evaluated a method of producing drugs from transgenic animals.¹²⁸ If it is approved, this drug may 'be followed by perhaps hundreds of others made from milk produced by genetically engineered goats, cows, rabbits and other animals. Other products in the pipeline are designed to treat people with hemophilia, severe respiratory disease and debilitating swollen tissues. The technique could make it cost-effective for companies to develop drugs to treat diseases that affect relatively few patients'.¹²⁹

The process involves inserting a human gene ('the DNA that codes for the human antithrombin protein') into 'the single-celled embryo of an animal',¹³⁰ so this seems to be a human-animal embryo.¹³¹ However, there is likely to be widespread acceptance of this

research because it could greatly reduce the price of manufacturing protein-based medications, which are notoriously expensive. Community attitudes may be affected by seeing that particular research has clear benefits (though creating a whole animal with some human genes is less problematic than creating embryos that are largely human).

At the same time, research that is 'contentious' will be under greater scrutiny than other research and scientists who want to create human-animal embryos may be pressed continually to justify their research in the light of its potential benefits. This is already happening in the UK. For example, a journalist writing in the Guardian said:

The magazine Science has judged reprogramming adult cells¹³² as the greatest scientific breakthrough of 2008 – from any area of science. ... In 2008 [Spanish] doctors used stem cells from bone marrow to create a whole new human organ – a trachea – for transplantation.¹³³ ... and what is more, it actually works. It is not all spin and vague promises. ... In marked contrast the Newcastle team [which has a license to create human-animal embryos] have taken cells from human embryos and created animal-human embryos' - but nothing else.¹³⁴

Moreover, even if a new ban is not imposed on the creation of human-animal embryos, it may become increasingly difficult for scientists to do this research. Regulatory bodies may not grant licenses because such research is not regarded as 'necessary';¹³⁵ ethics committees may not approve the research and embryo donors may not consent;¹³⁶ government funding agencies may prefer to allocate research funds to other projects;¹³⁷ and private investors may be concerned about potential profits if there are difficulties in patenting genetically modified animals and substances they produce.¹³⁸

In my view, it is not necessary to have a legislative ban on the creation of human-animal embryos – or transgenic embryos. The main concern that people have about these activities is the possibility that a creature will be created that is half human and half animal. The law in many jurisdictions rightly guards against that happening by legislation preventing the development of embryos formed for research beyond 14 days and attempts to implant such an embryo into a human or an animal.

Conclusion

It can be seen from the brief account of recent developments in human stem cell research that scientists have made considerable progress over the last few years towards forming stem cells from embryos and from body cells, and also differentiating those cells into other kinds of cells. Although no human stem cells have yet been derived from human embryos produced by somatic cell nuclear transfer, that research has only recently been permitted and it is in the early stages. Routine stem cell treatment is likely to be some time away in humans but there have been significant developments in animals. The limited availability of donated human eggs is one factor limiting embryo research. This could be overcome by allowing human genetic material to be inserted into animal eggs to obtain stem cells for

research. That is already being done in the UK but, again, this research is in the early stages.

However, future developments in science - and the ethical and legal responses - will depend on which avenue of research ultimately proves the most promising. President Obama has given his strong support to research on a greater range of human embryonic stem cells, saying that he hopes that 'Congress will act on a bi-partisan basis to provide further support for this research', where it is 'both scientifically worthy and responsibly conducted' under 'strict guidelines'.¹³⁹ Many scientists have been delighted about the new Executive Order.¹⁴⁰ President Obama has also supported other research 'to convert ordinary human cells into ones that resemble embryonic stem cells'.¹⁴¹ We do not know which avenue of research will be most successful, but, as President Obama has said, we should '[protect] free and open inquiry'.¹⁴²

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- ⁵¹ *Bio-Medicine Business Wire*. 2007. Research Indicates Geron's Human Embryonic Stem Cell-Based, Therapeutic for Spinal Cord Injury Evades Direct Attack by the Human Immune System. <http://www.bio-medicine.org/medicine-technology/Research-Indicates-Gerons-Human-Embryonic-Stem-Cell-Based-0ATherapeutic-for-Spinal-Cord-Injury-Evades-Direct-Attack-by-the-0AHuman-Immune-System-357-1/> (accessed March 6, 2009).
- ⁵² Baker, M. February 20, 2009. *Nature.com*. FDA puts plan for a neural stem cell trial on hold. http://blogs.nature.com/reports/theniche/2009/02/fda_puts_plan_for_a_neural_ste_1.html (accessed March 6, 2009); Stem cell 'cure' boy gets tumour. *BBC News*, February 18 <http://news.bbc.co.uk/2/hi/health/7894486.stm> (accessed March 6, 2009).
- ⁵³ http://www.wypr.org/MD_MORNING.html Radio interview, *Maryland Morning*. Growing the Embryonic Stem Cell Industry. 4 February 2009. (accessed February 11, 2009).
- ⁵⁴ Pilcher, H. Green light for UK stem-cell trial. Stroke patients to be treated with tailor-made brain cells. Published online 19 January 2009, *Nature*, doi:10.1038/news.2009.41 <http://www.nature.com/news/2009/090119/full/news/2009.41.html> (accessed March 6 2009); ReNeuron http://www.reneuron.com/news_events/document_178_237.php (accessed March 10, 2009).
- ⁵⁵ *Medical News Today*. 7 February 2009. Blood Clotting Drug ATyrn From Genetically Engineered Goats Approved By FDA. <http://www.medicalnewstoday.com/printerfriendlynews.php?newsid=138241> (accessed March 10, 2009).

⁵⁶ Canadian Institutes of Health Research, *Guidelines for the use of stem cells*, March 2001. The guidelines have been updated several times, with the latest revision published on June 29 2007:

<http://www.cihr.ca/e/34460.html> (accessed March 6, 2009)

⁵⁷ Research involving Human Embryos Act 2001 (Cth). Some states also have legislation; e.g. Assisted Reproductive Treatment Act 2008 (Vic).

⁵⁸ British Fertility Society. http://www.britishfertilitysociety.org.uk/practicepolicy/documents/07-07_BFS%20final%20submitted%20response%20to%20hybrid%20consultation%20MH.pdf. (accessed March 6, 2009).

⁵⁹ Ibid.

⁶⁰ In August 2001, President Bush barred the National Institutes of Health from funding research on embryonic stem cells other than that using 60 cell lines existing when he signed an Executive Order to that effect. Professor Doug Melton was reportedly frustrated by the limit of 'a few dozen cell lines of questionable quality, and, with private funding developed 'more than 70 ones... [of which] he distributed 3,000 copies to scientists round the world for

free': Park, A. The quest resumes. *Time*. Feb 9, 2009. pp 41-2 Som, N. Dec 2008. The Obama effect on stem cell research, BioSpectrum, [/www.biospectrumasia.com/content/041208IND7906.asp](http://www.biospectrumasia.com/content/041208IND7906.asp) (accessed March 6, 2009).

⁶¹ McCullough, M. Obama keeping stem-cell advocates waiting. *The Philadelphia Inquirer*. February 3, 2009. http://www.philly.com/inquirer/health_science/daily/20090203_Obama_keeping_stem-cell_advocates_waiting.html (accessed March 6, 2009)

⁶² In 2007, President Bush issued Executive Order 13435 requiring the Department of Health and Human Services to develop guidelines for funding alternative methods of research. *Weekly Compilation of Presidential Documents*, 43 22 June 2007, p. 821

⁶³ NIH Stem Cell information website. May individual states pass laws to permit human embryonic stem cell research? <http://stemcells.nih.gov/info/faqs.asp> (accessed March 6, 2009).

⁶⁴ Stem Cell Research Enhancement Act 2007. <http://www.govtrack.us/congress/bill.xpd?bill=s110-5&tab=summary> (accessed March 6, 2009).

⁶⁵ Som, note 59 above.

⁶⁶ According to an internet report, five states have introduced bills 'affirming the personhood rights of pre-born humans from the moment of fertilization': Maryland; North Dakota; Montana; South Carolina; and Alabama. Oregon and Mississippi have reportedly planning similar action. 'Seven States Have Launched Efforts for Personhood Rights for Pre-born - More Expected'. *LifeSite News.Com*. Feb 18, 2009. <http://www.lifesitenews.com/ldn/2009/feb/09021803.html> (accessed March 6, 2009). The Montana Personhood Amendment, SB 406, passed 26 to 24 in the Montana State Senate on February 26, 2009, states that 'all persons are born free and have certain inalienable rights ... person means a human being at all stages of human development of life, including the state of fertilization or conception, regardless of age, health, level of functioning, or condition of dependency':

Katie Walker. Personhood Amendment Passes Montana Senate. *Reuters*. February 27, 2009.

www.reuters.com/article/pressRelease/idUS95026+27+February+2009+PRN20090227 (accessed March 18, 2009).

⁶⁷ Quoted by Knight, M. Scientist: Stem cells could end animal testing. December 23, 2008; <http://edition.cnn.com/2008/HEALTH/12/22/stem.cell.drug.tests/> (accessed 6 March, 2009) Alice Park refers to a 'byzantine system of labeling and cataloguing'. The quest resumes, *Time*, February 9, 2009, p 41.

⁶⁸ Press release, the White House, March 9, 2009. http://www.thewhitehouse.gov/the_press_office/Remarks-Of-The-President-As-Prepared-For-Delivery-Signing-Of-Stem-Cell-Executive-Order-And-Scientific-Integrity-Presidential-Memorandum (accessed March 18, 2009)/

⁶⁹ Brown, C. Jan. 2009. Obama may not lift stem cell limits. *Politico*.

<http://politico.com/news/stories/019.17540.html> (accessed March 6, 2009)

⁷⁰ McCullough, M. Obama keeping stem-cell advocates waiting. *The Philadelphia Inquirer*. February 3, 2009. http://www.philly.com/inquirer/health_science/daily/20090203_Obama_keeping_stem-cell_advocates_waiting.html (accessed March 6, 2009).

⁷¹ Ibid. If the Dickey-Wicker amendment is not repealed, the Obama Directive may be challenged in the courts, though the outcome is debatable because 'research on already derived cells does not destroy embryos': Wadman, M. Stem-cell inaction prompts concern. *Nature*, 24 February 2009:

<http://www.nature.com/news/2009/090224/full/4571068a.html> (accessed March 10, 2009). Susan Solomon, CEO of the New York Stem Cell Foundation, states, '[President Obama] cannot single-handedly green-light federal funding to create [embryonic] stem cell lines themselves ... because Congress in 1996 banned the use

of human embryos, even those discarded in fertility clinics or voluntarily made for scientific purposes, for research purposes – including the creation of embryonic stem cells’. Solomon, S.L. Patients before politics: putting science first. *The Huffington Post*. March 9, 2009. http://www.huffingtonpost.com/susan-l-solomon/patients-before-politics_b_173084.html (accessed March 18, 2009).

⁷² Some ‘Church experts’ apparently have given ‘tentative statements of support’ to ‘techniques including “altered nuclear transfer” and “oocyte-assisted reprogramming” which using an unfertilized human egg and the nucleus of another cell, replace or reprogram genes so that pluripotent stem cells — those that can develop into any bodily tissue — are produced, but not a human embryo’: Thavis, J. Vatican underlines human cloning immorality. Sacrificing embryonic life for therapeutic ends ‘gravely immoral’. *Catholic News Service*. January 19, 2009. <http://www.wcr.ab.ca/news/2009/0119/cloning011909.shtml> (accessed March 6, 2009)

⁷³ Lehrman, S. Dolly’s Creator Moves Away from Cloning and Embryonic Stem Cells. *Scientific American*. July 2008. <http://www.sciam.com/article.cfm?id=no-more-cloning-around> (accessed March 6, 2009).

⁷⁴ Eggan, K., quoted by Johnson, C. Note 23 above: compare, Stem cells: FAQs. *CBC News Canada*. 7 Jan 2009. <http://www.cbc.ca/health/story/2009/01/07/f-stemcells.html> (accessed March 6, 2009): ‘researchers at the Harvard Stem Cell Institute say reprogrammed cells won’t eliminate the need or value of studying embryonic stem cells’.

⁷⁵ Hall, H. Japanese Stem Cell Scientist Announces Promising Results, *Business Week*, Feb 3, 2009. http://www.businessweek.com/globalbiz/blog/eyeonasia/archives/2009/2/japanese_cell_c.html?campaign_id=rss_blog_asiatech (accessed March 6, 2009).

⁷⁶ Clark, S.S. Induced pluripotent stem cells steal limelight from embryonic stem cells. January 5, 2009. <http://wistechology.com/articles/5331/> (accessed 6 March 2009). Clark adds in a later comment on the site that his prediction that ‘ESCs will likely find clinical use before iPS cells do’ has ‘become reality’ with the FDA approval of Geron’s trial of HES cells to treat spinal cord injuries.

⁷⁷ See notes 52-53 above and accompanying text.

⁷⁸ Clarke, note 76 above.

⁷⁹ Clarke, *ibid.* (Clarke’s paraphrase).

⁸⁰ Clarke, *ibid.* (Clarke’s paraphrase).

⁸¹ Clarke, *ibid.* quoting Mummery.

⁸² Knight, M. Scientist: Stem cells could end animal testing. December 23, 2008 <http://edition.cnn.com/2008/HEALTH/12/22/stem.cell.drug.tests/> (accessed March 6, 2009).

⁸³ Radio interview, *Maryland Morning*. Growing the Embryonic Stem Cell Industry. February 4, 2009. http://www.wypr.org/MD_MORNING.html (accessed February 4, 2009). Geron plans to recruit subjects who have had a crushed but not severed spinal tube, within 7 – 14 days after the injury: *ibid.*

⁸⁴ Leslie Metzler, University of Maryland School of Law, Radio interview, *Maryland Morning*. Note 83 above.

⁸⁵ The Vatican document, *Dignitas Personae* (The Dignity of a Person), Dec 2008 confirms the policy of the 1995 encyclical, *Evangelium Vitae* (The Gospel of Life): ‘To create embryos with the intention of destroying them, even with the intention of helping the sick, is completely incompatible with human dignity because it makes the existence of the human being at the embryonic stage nothing more than a means to be used and destroyed’ (para 30). http://www.usccb.org/comm/Dignitaspersonae/Dignitas_Personae.pdf (accessed March 10, 2009)

⁸⁶ Human Fertilization and Embryology Act 1990, Sch 2, para 3(1)(a); compare Council of Europe, *Convention on Human Rights and Biomedicine*, Article 18(2): ‘The creation of human embryos for research purposes is prohibited’.

⁸⁷ Research involving Human Embryos Act 2001 (Cth) ss 10A, 11. There is a limited exception where a human egg may be fertilized by a human sperm for research on the process of fertilization, but the process must stop as soon as fertilization is complete: s 7(1) (definition of ‘human embryo’, para (a)). This research is needed to investigate the efficacy of new methods of oocyte maturation. It may be possible to artificially mature human eggs taken from women who are not ovulating at the time of donation, or from donated ovarian tissue or from cadavers, but it is not possible to test whether such artificially matured eggs can be fertilized without actually fertilizing them.

⁸⁸ It is true that a ‘sperm-egg embryo’ is made up of genetic material from both parents equally whereas an ‘SCNT embryo’ has genetic material mostly from the person whose body cell was used to form the embryo, with only a small amount of mitochondrial DNA from the donated egg used to incubate that genetic material. However, that difference does not seem morally significant where the donors are not intentionally trying to combine their DNA to have a child. Where both donors are in an IVF program, their view of an embryo

formed from their own gametes which may be different from the views of donors of eggs and sperm separately.

⁸⁹ Michael Soules, President, American Society of Reproductive Medicine, quoted by Friend, T. *USA Today*, November 11, 2001. <http://cmbi.bjmu.edu.cn/news/0107/89.htm> (accessed March 10, 2009).

⁹⁰ These unlawful activities may, of course, still be undertaken, regardless of the legal sanctions. However, the law can only do what it can – stating what is unlawful and imposing strict penalties for noncompliance.

⁹¹ Though George Smith mentions ‘considerable concern and fear that some hybrid embryos could well be transferred to wombs of women’: *ibid*, note 1 above. No examples are given of who has expressed this ‘concern’.

⁹² Human Reproductive Cloning Act 2001. Therapeutic cloning (SCNT) is permitted under license under the Human Fertilization and Embryology Act 1990:

http://www.redorbit.com/news/science/65128/uk_scientists_apply_for_human_cloning_license/index.html (accessed March 6, 2009). Permission must be obtained from the Human Fertilization and Embryology Authority in order to perform or attempt SCNT. The first license was granted on August 11, 2004 to researchers at the University of Newcastle to allow them to investigate treatments for diabetes, Parkinson's disease and Alzheimer's disease.

⁹³ [Act Respecting Assisted Human Reproduction and Related Research 2004 s 5\(1\)](http://laws.justice.gc.ca/en/A-13.4). <http://laws.justice.gc.ca/en/A-13.4> (accessed March 10, 2009).

⁹⁴ The Gene Technology Act 2000 (Cth), which preceded the specific legislation on human cloning and embryo research and dealt principally with genetic modification of agricultural crops, included a provision that a person must not ‘knowingly or recklessly undertake an activity which will result in the cloning of a whole human being’ (s 192B). A similar prohibition has been inserted into subsequent Australian federal and state legislation, with the drafting becoming increasingly complex in its attempts to define ‘cloning’ and ‘genetically identical’. The Prohibition of Human Cloning Act 2001 (Cth) s 8(2) now states that a ‘genetic copy’ of another living or dead human can be established ‘if the set of genes in the nuclei of the cells of the living or dead human has been copied ...’.

⁹⁵ The Council of Europe's *Convention on Human Rights and Biomedicine* and its *Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings* appear to ban not only reproductive cloning but also SCNT. Of the Council's 45 member states, the Convention has been signed by 31 and ratified by 18. The Additional Protocol has been signed by 29 member nations and ratified by 14. The national laws of some European countries also ban reproductive cloning. In March 2005, the General Assembly of the United Nations adopted a declaration on human cloning: Arsanjari, M.H. Negotiating the UN Declaration on Human Cloning, *The American Journal of International Law*. <http://www.jstor.org/pss/3518835> (accessed March 10, 2009). Although the declaration is not legally binding, the words in ‘prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life’ may include SCNT, depending on interpretation: Smith, W. The U.N. on Cloning: Ban It. The United Nations speaks out against human cloning. *The Weekly Standard*, March 15, 2005.

<http://www.discovery.org/scripts/viewDB/index.php?command=view&id=2465&program=Bioethics&printerFriendly=true> (accessed March 10, 2009).

⁹⁶ In 1998, 2001, 2004 and 2007 the US House of Representatives voted whether to ban all human cloning, both reproductive and therapeutic. Each time, divisions in the Senate over therapeutic cloning prevented any proposal (a ban on both forms or on reproductive cloning only) from passing. The Human Cloning Prohibition Bill 2009 was introduced into the Senate on 6 Jan 2009. If passed, that bill would prohibit human cloning; and also receiving or importing a product of human cloning for any purpose. It would not prevent SCNT and other cloning techniques for research.

⁹⁷ A table of most US State laws is available at <http://www.ncsl.org/programs/health/Genetics/rt-shcl.htm> (accessed March 6, 2009).

⁹⁸ 2005 Senate Enrolled Act No. 2. 68.

⁹⁹ California was listed number four in the ‘top five stem-cell institutes globally’ in a review by technology consultants Cels. Corbyn, Z. UK's reputation as world leader in stem-cell research challenged. *Times Higher Education*. January 22, 2009.

<http://www.timeshighereducation.co.uk/story.asp?sectioncode=26&storycode=405090&c=1> (accessed March 6, 2009). Others in the top five were 1. Harvard; 2. Stanford; 3. Washington; and 5. Johns Hopkins.

¹⁰⁰ See top listed institutions, note 99 above. For example, in July 2008, GlaxoSmithKline reportedly entered into a \$25 million-plus agreement with the Harvard Stem Cell Institute: Mathew Knight. Scientist: Stem cells

could end animal testing. 23 Dec 2008. <http://edition.cnn.com/2008/HEALTH/12/22/stem.cell.drug.tests/> (accessed March 6, 2009).

¹⁰¹ The DNA of the 'cloned' child is not 'identical' to that of this person because the embryo also contains mitochondrial DNA from the egg used to incubate the nucleus from the person being 'cloned'.

¹⁰² For discussion of this technology and reasons why it might be used, see: Skene, L. 2008. Deriving sperm and eggs from human skin cells: facilitating community discussion. *Journal of Contemporary Health Law and Policy* 25(1); 76-82.

¹⁰³ DeNoon, D.J. Rejuvenated skin cells make stem cells. Adult cells turned back into embryo-like stem cells. *WebMD Health News*. Nov 20, 2007. Medicine.Net.com.

<http://www.medicinenet.com/script/main/art.asp?articlekey=85385> (accessed March 9, 2009).

¹⁰⁴ Multiple Sclerosis Resource Center. UCLA stem cells scientists make electrically active motor neurons from iPS cells. 25 February 2009.

<http://www.msrmc.co.uk/index.cfm?fuseaction=show&pageid=1826> (accessed March 10, 2009).

¹⁰⁵ Professor Shinya Yamanaka of Kyoto University reportedly said that 'it may also be possible to grow egg and sperm cells for infertility treatments, which raises the controversial possibility of growing eggs from men and sperm from women so that same sex couples could conceive a baby': Highfield, R. Stem cell research revolution spells end for therapeutic cloning. *Telegraph*. Nov 10, 2008.

<http://www.telegraph.co.uk/scienceandtechnology/science/sciencenews/3315273/Stem-cell-research-revolution-spells-end-for-therapeutic-cloning.html> (accessed March 10, 2009). In a comment on the same site, Professor Alta Charo, University of Wisconsin-Madison Professor of Law and Bioethics says: 'This is a method for creating a stem cell line without ever having to work through, at any stage, an entity that is a viable embryo'.

¹⁰⁶ Hinxton Group. The Science, Ethics and Policy Challenges of Pluripotent Stem-Cell Derived Gametes. April 11, 2008. http://www.hinxtongroup.org/au_pscdg_cs.html (accessed March 10, 2009); Skene, note 102 above.

¹⁰⁷ Presentations at the Hinxton Group meeting, Hinxton, April 11, 2008.

¹⁰⁸ According to an Australian newspaper report, 227 sheep eggs were used to create Dolly and 304 monkey eggs to create the first reported 'cloned' primate: Martin, J. Amen to death of embryo research. *Australian*. Jan 17, 2008. In Chinese research reported in 2009 creating patient-specific ES cells, 'a total of 135 oocytes were obtained from 12 healthy donors (30-35 years)': Chinese Researchers Make Cloned Human Blastocysts *CellNEWS*. February 3, 2009. http://cellnews-blog.blogspot.com/2009_02_01_archive.html (accessed March 10, 2009).

¹⁰⁹ UK: Policy of the Human Fertilization and Embryology Authority (HFEA) - *Seed Review*, 2004; Canada: Assisted Human Reproduction Act 2004 (Can); Canadian Institutes of Health Research, Guidelines for the use of stem cells, March 2001 (the guidelines have been updated several times, with the latest revision published on June 29, 2007); Australia: Prohibition of Human Cloning Act 2002 (Cth) s 23.

¹¹⁰ Some states, however, have legislative restrictions on the sale of eggs for use in research. California, for example, prohibits the purchase or sale of an ovum, zygote, embryo, or fetus for the purpose of cloning human beings.

¹¹¹ Isasi, R.M., Knoppers, B.M. Monetary payments for the procurement of oocytes for stem cell research: In search of ethical and political consistency. (2007) 1 *Stem Cell Research* 37.

¹¹² The ethical distinction is blurred: Hyun, I. Fair payment or undue inducement? (2006) 442 *Nature* 629-630.

¹¹³ American Society of Reproductive Medicine (ASRM) Ethics Committee, Financial incentives in recruitment of oocyte donors, (2000) 74 *Fertil Steril* 216-220.

¹¹⁴ George Smith states that 'some women obtain upwards of \$75,000 in the open market for their eggs to be used [in IVF]': Smith, note 1 above, p. 149.

¹¹⁵ ASRM, note 113 above, p. 219.

¹¹⁶ Covington, S.N., Gibbons, W. What is happening to the price of eggs? (2007) 87 *Fertility and Sterility* 1001-1004.

¹¹⁷ Macklin, R. On paying money to research subjects: 'due' and 'undue' inducements, (1981) 3 *IRB: Ethics and Human Research* 1-6.

¹¹⁸ Bentley, J.P., Thacker, P.G. The influence of risk and monetary payment on the research participation decision making process (2004) 30 *Journal of Medical Ethics* 293-298.

¹¹⁹ Quoted by Singer, E. Human Therapeutic Cloning at a Standstill. *Technology Review*, October 9, 2007. http://www.genpol.org/PDF_News_Archive/news100907tr.pdf (accessed March 10, 2009).

¹²⁰ Ibid.

¹²¹ Prohibition of Human Cloning Act 2002 (Cth) s 20.

¹²² Assisted Human Reproduction Act 2004 (Can) s 5(1)(i),(j),

¹²³ Henderson, M. We have created human-animal embryos already, says British team. *The Times*, April 2, 2009, 2.

http://www.timesonline.co.uk/tol/life_and_style/health/article3663033.ece (accessed March 6, 2009)

¹²⁴ Human Fertilization and Embryology Authority. HFEA Chair welcomes Royal Assent for HFE Act. Nov 15, 2008. <http://www.hfea.gov.uk/en/1746.html> (accessed March 6, 2009); Lovell-Badge, R. The regulation of human embryo and stem-cell research in the United Kingdom. (2008) 9 *Nat Rev Mol Cell Biol* 998-1003. The human-animal hybrid embryos that may be created under license are: cybrids (or cytoplasmic hybrids): formed by 'incubating' human genetic material in cytoplasm from an animal; transgenic embryos: formed by introducing animal DNA into one or more cells of a human embryo; chimeras: formed by adding one or more animal cells to a human embryo; hybrid embryos: formed from a human egg and animal sperm or vice versa; or from an animal pro-nucleus and a human pro-nucleus: Human Fertilization and Embryology Act 1990, s 4A(5). Creating a 'true hybrid' by fertilizing a human egg with animal sperm or vice versa is unlawful. <http://www.guardian.co.uk/science/2007/may/17/businessofresearch.medicineandhealth> (accessed March 6, 2009).

¹²⁵ The human-animal hybrid embryos that may be created under license are: cybrids (or cytoplasmic hybrids): formed by 'incubating' human genetic material in cytoplasm from an animal; transgenic embryos: formed by introducing animal DNA into one or more cells of a human embryo; chimeras: formed by adding one or more animal cells to a human embryo; hybrid embryos: formed from a human egg and animal sperm or vice versa; or from an animal pro-nucleus and a human pro-nucleus: Human Fertilization and Embryology Act 1990, s 4A(5). Creating a 'true hybrid' by fertilizing a human egg with animal sperm or vice versa is unlawful. <http://www.guardian.co.uk/science/2007/may/17/businessofresearch.medicineandhealth> (accessed March 6, 2009).

¹²⁶ Research to date suggests that animal eggs could not be used to generate patient-specific stem cells 'without appropriate reprogramming' (emphasis added): Keim, B. Research Breakthrough: Human Clones May Be Genetically Viable. Feb 2, 2009. <http://blog.wired.com/wiredscience/2009/02/human-clones-ap.html> (accessed March 6, 2009); Chung, Y., Bishop, C.E., Treff, N.R., Walker, S.J., Sandler, V.M., Becker, S., Klimanskaya, I., Wun, W-S., Dunn, R., Hall, R.M., Su, J., Lu, S-J., Maserati, M., Choi, Y-H., Scott, R., Atala, A., Dittman, R., Lanza, R. Reprogramming of Human Somatic Cells Using Human and Animal Oocytes. *Cloning and Stem Cell*. 11 (2) Feb. 1, 2009. However, the futility of using animal eggs has been questioned by other scientists: Elie Dolgin, Animal eggs no good for cloning? *The Scientist*, 2 Feb 2009. <http://www.the-scientist.com/news/display/55392/> (accessed March 6, 2009).

¹²⁷ The Lockhart Committee recommended to the Australian federal government in 2005 that this test should be permitted: *Reports, Legislation Review: Prohibition of Human Cloning Act 2002 and Research Involving Human Embryos Act 2002*, Recommendation 17, p xxiii. http://www.nhmrc.gov.au/research/embryos/review/_files/legislation_review_reports_full_doc_19dec05.pdf (accessed March 6, 2009). The Prohibition of Human Cloning for Reproduction Act 2002 (Cth) now permits the test: see s 23B, note (a).

¹²⁸ Rowe, A. FDA to Evaluate Drugs Made by Genetically Modified Goats. Jan 8, 2009: <http://blog.wired.com/wiredscience/2009/01/drugsfromgoats.html> (accessed March 6, 2009).

¹²⁹ Kaplan K. New old-fashioned drug makers: goats. January 10, 2009. <http://www.latimes.com/news/nationworld/nation/la-sci-geneticmilk10-2009jan10.0.242781.story> (accessed March 6, 2009).

¹³⁰ Ibid, quoting Thomas Newberry, the vice president of GTC Biotherapeutics, the company that has developed the drug. According to Rowe, 'the drug is already on the European market, but if approved, it will be the first medication made by a GM animal to be sold in the United States': ibid.

¹³¹ Though Newberry says that 'Our technology simply provides an extra bit of coding so the mammary gland also makes a protein with human therapeutic value': ibid.

¹³² Quoting report on reprogramming adult cells. <http://www.aaas.org/news/releases/2008/1218breakthrough.shtml>. (accessed March 4, 2009).

¹³³ See report of UK Stem Cell network, A stem cell success story - UK stem cell biologists help to deliver a new bronchus for Claudia Castillo. http://www.uknscn.org/downloads/newsletter_winter08.pdf (accessed March 10, 2009).

¹³⁴ Jones, D. Should we allow research using human-animal hybrid embryos? 'Nothing but a sideshow'. Jan 16, 2009: <http://www.guardian.co.uk/commentisfree/belief/2009/jan/16/ethics-stemcells> (accessed March 10, 2009).

¹³⁵ Though Jones notes that ‘The HFEA which issued these licences has the extraordinary record of never having ultimately refused a research licence in all its 20 years’: *ibid.*

¹³⁶ Jones states with regard to the Newcastle team, ‘it seems to have been done without permission from the couple who donated the original embryo. Some of their DNA has been put into cow eggs without their consent. Would you be happy about this?’ *Ibid.*

¹³⁷ Two groups at King’s College London and Newcastle University have reportedly had grant applications to create hybrid embryos rejected, ‘forcing [them] to consider putting the research on hold’: Sample, I. Rival stem cell technique takes the heart out of hybrid embryo debate. *Guardian*. January 13, 2009.

<http://www.guardian.co.uk/science/2009/jan/13/hybrid-embryos-stem-cells> (accessed March 10, 2009), Instead, funding agencies are financing IPS cell research with the latest figures from the Medical Research Council showing that funding for adult stem cells, which includes IPS cells, rose sharply last year as a proportion of all stem cell research, from 46% to 61.3%: *ibid.* Harry Moore, head of reproductive biology at Sheffield University reportedly said that the reason for this shift is clear: ‘What has happened is the field has moved on. You could argue that IPS cells are a more important area than hybrids now’: *ibid.* However, Sir Leszek Borysiewicz, chief executive of the Medical Research Council, reportedly said that grants are based on peer review which ‘rules out the possibility of a personal moral view influencing the final outcome of a proposal’: *ibid.*

¹³⁸ George Smith notes under the heading ‘Encouraging Experimentation’ that ‘there are more than 100 patent applications related to products of genetic engineering: Smith, note 1 above, pp. 60, 92 (n 114).

¹³⁹ Note 68 above. Relevant guidelines include the International Society for Stem Cell Research (ISSCR), *Guidelines for the Conduct of Human Embryonic Stem Cell Research*, February 7, 2007.

<http://www.isscr.org/guidelines/index.htm> (accessed March 10, 2009);

<http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf> (accessed March 10, 2009).

¹⁴⁰ International Society for Stem Cell Research (ISSCR). ISSCR Scientists Elated for Future of Human Embryonic Stem Cell Research After Obama Lifts Funding Ban. March 9, 2009.

http://www.isscr.org/press_releases/obama_repeals.html (accessed March 18, 2009).

¹⁴¹ *Ibid.*

¹⁴² Note 68 above.