Therapeutic Cloning for Tissue Repair

Report from a Forum held on

16 September 1999

Australian Academy of Science

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Specialised terminology, when not explained in the text of this report, will be found in the glossary.

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The Australian Academy of Science hosted a second consultative Forum on *Therapeutic Cloning for Tissue Repair*, on September 16, 1999. The meeting was planned to contribute to ongoing community discussion on human embryonic stem cell (ES cell) research. The objective is to realise the therapeutic benefits of human stem cell research in ways that the community finds acceptable.

It is the promise of new cures for debilitating diseases that has stimulated intense research interest in stem cells. Stem cells are not only able to reproduce themselves, but also have the potential to revitalise damaged tissues and organs.

Stem cells are constantly renewing certain parts of the human body. They replenish blood, mend the lining of the gut and renew skin cells, even in adults. This is nature healing itself. But nature does not repair all tissues and organs damaged by disease, by injury or by ageing. Nerve cells damaged in Parkinson's disease, by stroke, by spinal injury or in Alzheimer's disease, cannot repair themselves. Nature does not cure heart disease, diabetes, liver disease or kidney failure.

But nature does have the *capacity* to rejuvenate adult cells, as shown by the reversal of the differentiation of these cells in the experiments which led to the cloning of sheep, cattle and mice. In cloning experiments, adult DNA has been reprogrammed to begin development once again.

Embryos contain versatile stem cells that can turn into almost any cell in the body. Embryonic stem cells were isolated from mice nearly 20 years ago, but isolation and maintenance of human ES cells remained elusive. These "ultimate human cells" have now been found, after many years of research. They were isolated from one-week old human embryos, called *blastocysts,* by scientists at the University of Wisconsin. ES cells have the potential to develop into nearly any cell type in the human body, including nerve, muscle and blood cells, but will not turn into a fetus because they do not have the capacity to develop a placenta.

Human ES cells were derived from donated embryos surplus to the requirements of patients undergoing infertility treatments. One other potential source of ES cells is through the application of cloning techniques, by substituting the nucleus from a human egg with the nucleus of an adult cell. This technique has proved successful in *reproductive cloning* of sheep, cattle and mice. The technique, if used to create stem cells intended for self-compatible tissue and organ repair, is known as *therapeutic cloning*. The Academy considers that human reproductive cloning is unethical and unsafe and should be prohibited, but that research in therapeutic cloning should be permitted.

The idea that ES cells hold great therapeutic promise, and that they could revolutionise medical treatments of degenerative diseases, is now widely accepted. It is also understood that therapeutic applications will be a long time in becoming a reality. But should human embryos be used for fundamental research that would lead to those therapeutic applications? Are there alternative approaches to use of ES cells in tissue repair?

The views expressed in this Forum Summary are those of the Australian Academy of Science and were endorsed at the Academy Council meeting on February 3rd 2000. The views do not necessarily reflect the views of Forum attendees. Abstracts of speakers' presentations may be accessed at **http://www.science.org.au/academy/media/clonabs.pdf**.

There were several important and recurring views expressed at the Forum. These were:

- ✓ that medical treatments of degenerative diseases may well be revolutionised by stem cell research, albeit in an unknown time-frame;
- ✓ that embryonic stem cell research in Australia is, at present, internationally competitive;
- ✓ that alternative approaches to tissue repair that do not involve human embryos may one day be a reality;
- ✓ that any research on human embryos should be regulated at the highest ethical standards, according to national guidelines that are mandatory for both publicly and privately-funded laboratories;
- ✓ that legislation is an imperfect vehicle for responding to the rapid changes in scientific procedures and techniques and to less rapid changes in public opinion;
- ✓ that national responses to developments in human stem cell research have been mixed;
- ✓ that community discussion on the risks and benefits of human ES cell research should be promoted by policy makers and by scientists.

The Australian Academy of Science was convinced by the quality of scientific presentations at the Forum, that Australia has the capacity to participate fully in the fundamental research that must be undertaken if stem cells are to achieve their potential for tissue repair. It is the responsibility of policy makers, scientists and the broader community to facilitate progress in research into tissue repair in ways that the community finds acceptable.

Medical treatments of degenerative diseases may well be revolutionised by embryonic stem cell research, albeit in an unknown time-frame.

It is little more than one year ago that an interesting piece of investigative journalism appeared in *Technology Review*, a journal of the Massachusetts Institute of Technology (MIT). The article described the search for the "Ultimate Cell", a human cell that could be coaxed, in the test-tube, to produce all types of tissue on demand. The article identified, world-wide, only a few research groups who acknowledged they were searching for the Ultimate Cell, for a human embryonic stem (ES) cell.

The July 1998 *Technology Review* editorial stated:

> The hunt for human ES cells must come out into the light. The stakes are too high for the hunt for human embryonic stem cells to remain behind closed doors.

Human ES cells have now been isolated, at laboratories at the University of Wisconsin, John Hopkins University and at the University of Singapore, in collaboration with Monash University. The doors have been opened by publications in the scientific press and by presentations at scientific conferences. How, then, are those "high stakes" to be realised?

Therapeutic applications of human ES cell research in tissue repair potentially include:

- therapeutic cloning for tissue repair;
- a generic ES cell for tissue repair;
- a "blood bank" of ES cells for tissue repair.

Therapeutic cloning for tissue repair

One human organ, skin, is readily cultured to provide replacement tissue for burns victims. Healthy skin cells from the patient can be grown rapidly *in vitro* to provide self-compatible skin grafts. This tailor-made, hospital-based treatment is very effective, but does not attract commercial interest because there is no patentable commercial product. In contrast, there is considerable interest among investors in a generic skin replacement product being developed jointly by the Australian Commonwealth Serum Laboratories and American Red Cross.

An analogy may be made between skin replacement therapy and therapeutic cloning for tissue repair. As in skin replacement therapy, the intent of therapeutic cloning would be to make cells that are genetically identical to the patient's tissues. The approach would be to combine ES cell technology with cloning techniques. The nucleus of a donated human egg would be replaced with the nucleus from an adult cell from the patient. The resulting embryo would be cultured for about one week to the 100 cell blastocyst stage, in order to obtain self-compatible ES cells.

Such an approach would need to be very much more efficient than is currently the case in experimental animals, because of severe limitations on the availability of donated human eggs. The success rate of cloning techniques may be expected to improve, but even so, it is unlikely that commercial interest would focus on expensive, patient-specific, hospital-based treatment, because, apart from certain reagents, there is no truly generic product.

A generic ES cell for tissue repair

Private investment is likely to be concentrated on producing generic tissue that could be used in treating a multitude of patients. One idea is that genetic engineering techniques could be used to disrupt the so-called transplantation genes that encode proteins on the surface of the cell and tag them as foreign. Once tagged as foreign, cells are subject to an immune attack, so any therapeutic procedures need to take this biological phenomenon into account.

In practice, it will be very difficult to create a generic donor ES cell without harming the cell itself. Further, a cell stripped of its surface antigen defence system will be vulnerable to infection.

A more likely situation is that generic cells could be used for certain types of tissue repair, for tissue where immune rejection is of lower risk. There is a hierarchy among tissues with respect to immune rejection. For bone marrow transplantation, there must be exquisite matching of transplantation antigens or else rejection of the foreign tissue will result. In contrast, for cornea transplantation, immune rejection of foreign tissue does not occur. The blood-brain barrier may provide the brain with special privilege with respect to transplantation, as suggested by the report that human fetal neurons can successfully implant and make appropriate connections in the rat brain.

A "blood bank" of ES cells for tissue repair

One other proposal that is a compromise between the patient-specific protocol and the generic donor ES cell approach is the possibility that a bank of ES cells, of various tissue antigen types, could be established. Although there are literally millions of different tissue antigen combinations among individuals, a bank of several hundred different ES cell types could cater for the most common antigen types.

Overview

In the United States of America, privately funded research in the area of human reproductive technologies is virtually unregulated. Private investment in human ES cell research will drive the international research agenda unless public-good applications are addressed by investment of public funds in ES cell research. Private investment in human ES cell research is likely to focus on cosmetic applications in common conditions where there is large market demand, rather than on therapeutic procedures for rare disorders. For example, tooth-buds and hair follicles have been identified among cell types developing from ES cells. Geron Corporation, San Francisco, a leader in stem cell research, has a particular interest in ageing.

A focus on cosmetic rather than on therapeutic applications of ES cell research may well alienate public opinion about ES cell research. It is important that a way be found to promote public investment in this area of research, before patents are in place that might impose undue restrictions on development of therapeutic applications.

Embryonic Stem cell research in Australia is internationally competitive.

Australian scientists described their current research and the future challenges in study of ES cells derived from non-human primates, humans and mice. In all cases, ES cell lines had been derived from the inner cell masses of blastocysts, not by therapeutic cloning.

Non-human primate ES cells

It took fifteen years after the first isolation of ES cells in mice for ES cells to be isolated in rhesus and marmoset monkeys. The reagents such as interleukin 6 that maintain mouse ES cells in their proliferating and undifferentiated state do not work in primate ES cells; new experimental embryology systems and reagents needed to be developed. The mouse is a good experimental model in some respects, with short generation times and cost-effective maintenance, but it is often a flawed model for primate biological systems, as is evident in the case of experimental embryology.

Development of non-human primate ES cells by a research team at the University of Wisconsin with strong links to the Australian National University defined the protocols for maintaining prolonged proliferation of primate ES cells, for confirmation of unique markers that identify ES cells, and for the demonstration that ES cells could develop into different types of tissue. This work established the experimental systems for derivation of ES cells from inner cell masses of human embryos cultured to the blastocyst stage.

Human ES cells

A joint initiative between the University of Singapore and Monash University has resulted in the world's second demonstration that ES cell lines can be derived from human blastocysts. The ES cells will differentiate into a range of cell types, either spontaneously or in response to specific culture conditions and factors. These cell types have characteristics of neuronal ganglia, lung epithelia, gut tissue, muscle cells, bone and cartilage, among others.

The research challenges are to identify and characterise the factors and conditions that maintain, expand and direct the lineages of the cell lines, to drive exclusive differentiation of cells into desired tissue types.

Mouse ES cells

Research at the University of Adelaide has applied knowledge gained from study of early mouse embryogenesis to direct mouse ES cells into homogeneous populations of differentiated cells. Soluble factors have been identified that convert ES cells homogeneously into primitive ectoderm, which can in turn be coaxed specifically into either ectoderm or mesoderm. These germ layer equivalents go on to form neural stem cells and neurons, and blood and muscle cells respectively. Purification of the soluble factors has permitted their functional and molecular characterisation. These factors have the ability to control differentiation and de-differentiation in a way that suggests ES cells do indeed have important therapeutic prospects in both tissue repair and as a vehicle for delivery of gene therapy.

Cloning technology in domestic livestock

In domestic livestock, reproductive cloning of animals from adult cells was first demonstrated in sheep in 1997 and has subsequently been demonstrated in goats, cattle, rabbits and mice. In domestic livestock there is interest in using cloning technology as a reliable way to develop transgenic animals which secrete human proteins of therapeutic benefit (e.g. blood-clotting factors) in milk; more than ten such products, such as alpha-1-antitrypsin for application in emphysema, are now in phase 1 clinical trials.

Domestic livestock, especially transgenic pigs, are of intense research interest in North America and Europe as a potential source of donors of organs for human patients. Concerns have been expressed about possible hazards arising from this research. Firstly, porcine virus DNA sequences may lie latent in the genomes of pigs but could possibly infect the human population if transferred to immuno-suppressed transplantation patients. Secondly, if transgenic pigs are genetically altered to make their tissue antigens more similar to those of humans, not only may humans become susceptible to porcine diseases, but also pigs may become a reservoir of infection for human diseases.

If the potential for human ES cell research could be realised, the research described in the two paragraphs above would be overtaken. Long-term prospects are that gene therapy could be delivered directly to patients with genetic disorders, negating the need for production of substitute human proteins in livestock. If the potential for tissue repair through use of therapeutic cloning could be achieved, the demand for xenotransplantation, with all its potential hazards, could be avoided.

Overview

All researchers speaking in the scientific session stressed the very many years of research invested in their current achievements. Progress in basic research seems, to the lay person, to be proceeding with breath-taking speed. But it can take years for scientists to carefully test new paradigms, to understand the full implications of experimental observations, to perfect techniques and to characterise the functional and molecular properties of factors that drive their experimental systems. Slow as it may be to acquire new scientific knowledge, application of that knowledge for clinical objectives is an even slower process. Although mankind may be on the threshold of harvesting the benefits of ES cell research, it will take time for the therapeutic potential of ES cell research to be fully realised.

There is a need for basic research to better understand ES cells, to understand cell lineage choice under different conditions and the ability of cells to integrate into new environments after transplantation. We need also to understand the potential risk that undifferentiated cells might become cancerous under certain conditions.

The Academy was convinced, by the quality of the scientific presentations, that Australian research into ES cells is internationally competitive, at present. Given the substantial investments elsewhere, it will be difficult to maintain the competitive edge unless this area of research receives adequate resources.

Alternative approaches to tissue repair that do not involve human embryos may one day be a reality. The understanding gained by study of growth factors and their receptors in ES cells may speed the demise of ES cell use in tissue repair.

Recent advances in molecular biology have increased our knowledge of the regulation of gene expression. This is maintained by continuously active control mechanisms whereby proteins bind to DNA sequences adjacent to genes, to turn them on and off. In theory, it should be possible to reprogram almost any adult DNA to begin earlier paths of differentiation.

Our knowledge of these processes is imperfect. Some Forum participants believed the problem of adult cell de-differentiation could be overcome with "a bit of hard work". Another view expressed was that without a keen understanding of the molecular and functional properties of factors that controlled early embryonic cell differentiation, reprogramming of adult cells would have serious technical limitations.

Alternative approaches to use of ES cells in tissue repair include:

- partial de-differentiation and reprogramming of adult cells;
- identification of growth factors that would stimulate scattered stem cells to mature;
- identification of factors in cytoplasm of the oocyte that rejuvenate the adult nucleus;
- tissue engineering.

Partial de-differentiation and re-programming of adult cells

Optimism regarding the possible re-programming of adult cells follows reports that human marrow cells behave like nerve cells when injected into the brains of rats. In the converse experiment, neural stem cells from the mouse brain, when transplanted in mice that have been irradiated to destroy host bone marrow cells produced a variety of blood cell types. However, some researchers suspect that the blood cells may have arisen not from neural stem cells but from a more primitive stem cell also present in the sample.

Yet another report has shown that human stem cells taken from adult marrow could be coaxed to differentiate exclusively into fat, cartilage or bone lineages. Different assay conditions, including variations in nutrients, cell density, and growth factors, determined the direction of differentiation.

Studies of adult stem cells in animal experimental models suggest that the de-differentiation of adult stem cells will be scientifically and technically limited and not all tissue and organs will be open to repair via this route. One major limitation may be the difficulty in accessing the anatomic source, such as the brain, with safety.

Identification of growth factors that would stimulate scattered stem cells to mature

Dispersed, partially-differentiated stem cells are known to exist in adult tissue and this has prompted some optimism that it may be possible to stimulate these adult stem cells to mature, to produce a variety of human tissues.

ES cell research may identify and characterise regulators of stem cell self-renewal and differentiation, so that those regulators could be delivered to damaged tissues and organs to stimulate maturation of any scattered stem cells. This approach may have application in certain diseases, but some tissues and organs, such as the heart and the islet cells of the pancreas that control diabetes, retain few or no stem cells.

Identification of factors in cytoplasm of the oocyte that rejuvenate the adult nucleus

At present, the only known way to deprogram the nucleus of an adult cell is to place it in an enucleated oocyte, as in cloning technology. This clumsy methodology reflects our poor state of knowledge about the myriad of factors present in the cytoplasm of the oocyte. The oocyte is known to be rich in a number of enzymes, such as telomerase, that may contribute to rejuvenation of the adult nucleus, but there are many additional regulators that remain to be identified and characterised at the molecular and functional level.

Tissue engineering

There has been recent progress in development of tissues, such as arteries and bladders, grown on biodegradable polymer matrices. Although engineered bladders and arteries are significant achievements, these hollow structures with relatively thin layers of cells are easier to prepare than other more complex organs that need networks of arteries, veins and capillaries, as well as nerves to regulate function. Success in engineering simple tissues does not mean, in any sense, that stem cell research has been overtaken.

Overview

Adult stem cells cannot adequately substitute for ES cells in basic research concerned with embryogenesis and developmental biology because important biological differences exist between embryonic and adult stem cells. However, research into adult stem cells should be encouraged, especially to permit rapid application of insights gained from study of ES cells, and because progress made in this area of research may inform the other.

One of the important prospects for ES cells is as a delivery vehicle for gene therapy, as alternative approaches to gene delivery have so far proved disappointing. Genetic modification of mouse ES cells is now routine in many genetic research laboratories, suggesting these techniques could have application in gene therapy for human patients with genetic disease, and in treatment of patients with life-threatening viral infections.

The Australian Academy of Science considers that the National Health & Medical Research Council should be asked to encourage research into stem cells obtained from adult organisms.

Research on human embryos should be regulated based on the highest ethical standards, according to national guidelines that are mandatory for both publicly- and privately-funded laboratories.

The 1999 *National Statement on Ethical Conduct in Research Involving Humans* regulates research conduct in Australia. This document, prepared by the Australian Health Ethics Committee (AHEC) and developed further by a joint working party of the Australian Vice-Chancellors' Committee, the Australian Research Council, AHEC and the learned Academies, sets the highest standards for conduct of research in Australia. It is both proscriptive, in protecting the human subjects of research, and aspirational in striving for the highest international standards in research. This document sets clear guide-lines for researchers and should ensure that the community has confidence in the quality, safety and ethical nature of any research protocols approved by Institutional Ethics Committees.

With respect to research involving human embryos, the National Code refers to the 1996 NHMRC *Ethical Guidelines on assisted reproductive technology.* These guidelines permit (6.3) non-therapeutic research which does not harm the embryo and (6.4) research on human embryos in exceptional circumstances, but do not permit (11.1) creation of an embryo for research purposes. Under Section 6.4 of the *Ethical Guidelines,*

6.4 Non-therapeutic research which involves the destruction of the embryo, or which may otherwise not leave it in an implantable condition, should only be approved by an IEC in exceptional circumstances.

Exceptional circumstances would arise where there is a likelihood of a significant advance in knowledge or improvement in technologies for treatment.

Under Section 11.1 of the *Ethical Guidelines,* application of therapeutic cloning techniques to produce a human embryo is not permitted:

The following practices are ethically unacceptable and/or should be prohibited:

11.1 developing embryos for purposes other than for their use in an approved ART treatment program.

The Forum was presented with criteria for judging the ethical acceptability of various procedures relating to use of human embryos in research. These criteria were applicable whether the embryos were surplus to *in vitro* fertilisation treatments or produced by cloning techniques.

Considerations included:

- the quality of the research, and potential gains for society and for individuals;
- the safety of the research procedures;
- religious views;
- respect for individuals regarding informed consent and privacy;
- containability of the procedure, so that it does not generate a 'slippery slope' towards objectionable procedures;
- the possibility of adequate regulation and control.

Analysis using these considerations shows human reproductive cloning to be unethical on safety grounds alone, whereas therapeutic cloning for tissue repair and ES cell research would be defined as an important issues for public debate.

Legislation is an imperfect vehicle for responding to the rapid changes in scientific procedures and techniques and to less rapid changes in public opinion.

Legislation is said to have advantages in that it is a clear statement of public values and expectations. It is systematic, gives powers of enforcement, and is consultative in promoting debate in the community and in parliament. Legislation need not be inflexible if provision is made for monitoring and review, but it is hard to change. It can provide national standards if there is a uniform approach by the States, as is the case for legislation regarding organ and tissue transplantation.

In the case of legislation regarding assisted reproductive technologies and research on human embryos, there is no consistency in Australian law. In the State of Victoria, legislation is based on the criminal model; it is a criminal offence to undertake any research on a human embryo. In South Australia and in Western Australia, legislation seeks to regulate assisted reproductive technologies with a statutory system of licensing of those who carry out the procedures. Legislation in these three States overrules the NHMRC *Ethical Guidelines in assisted reproductive technologies,* which regulate research and clinical practice in other Australian States.

The difficulty of effectively legislating in an area of rapidly developing technologies is apparent from examination of the laws in Victoria, South Australia and Western Australia. In Victoria, said to have the most stringent legislation in the world regarding human embryo research, it is legal to undertake research on human ES cell lines, whereas in Western Australia, it is not. In South Australia, creation of genetically identical embryos by embryo splitting is banned, but reproductive cloning to produce a human fetus by somatic cell nuclear transfer would not be illegal.

Some Forum participants considered it appropriate to use legislation to set limits on certain research practices, such as prohibiting the cloning of human fetuses, but not to regulate the details of research practice. A common view was that human ES cell research should be subject to regulation under the law in such a way as to take account of the rapid development of new technologies and the changing applications of those technologies. A national panel of experts should be charged with advising on regulation and State laws should be reviewed to apply a more consistent application of national standards.

The need for national oversight of human ES cell research, rather than local oversight, is crucial if the public is to be assured that any work in human stem cell research is of the highest scientific standard, is safe, and is ethically acceptable. In Australia, the regulatory system has worked well in those States without legislation regarding assisted reproduction and embryo research, with both privately and publicly-funded clinics and laboratories guided by the standards set by the NHMRC.

The Australian Academy of Science supports the view put forward that regulation within a uniform, national legislative framework can provide the accountability in research that the public demands.

National responses to scientific developments in human ES cell research have been mixed.

Some countries have legislation in place (originally enacted to ensure ethical practices in fertility clinics), that imposes particular restrictions or prohibitions on the use of human embryos for research. In some other countries, such as Singapore, research on donated embryos surplus to requirements in fertility clinics is permitted if the embryo has developed for no longer than 14 days.

National responses of particular interest to the Forum were those from:

- Australia;
- United Kingdom;
- United States of America.

Australia

The Australian Health Ethics Committee (AHEC) provided the Minister for Health and Aged Care with advice on *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings* in December 1998.

AHEC recommends that:

- the Commonwealth Government, through the Minister for Health and Aged Care, reaffirm its support for the UNESCO *Declaration on the human genome and human rights*;

- noting that Victoria, South Australia and Western Australia have legislation regulating embryo research and prohibiting the cloning of human beings, the Minister for Health and Aged Care should urge the other States and Territories to introduce legislation to limit research on human embryos according to the principles set out in Sections 6 and 11 of the NHMRC *Ethical Guidelines on assisted reproductive technology;*

- noting that there are statutory authorities established in Victoria, South Australia and Western Australia which consider and may approve human embryo research under strict conditions, the Minister for Health and Aged Care should urge the remaining States and Territories to establish similar statutory authorities with power to regulate research on human embryos according to the principles set out in Sections 6 and 11 of the NHMRC *Ethical Guidelines on assisted reproductive technology;* and

- the Minister for Health and Aged Care should encourage and promote informed community discussion on the potential therapeutic benefits and possible risks of the development of cloning techniques.

The House of Representatives Standing Committee on Legal and Constitutional Affairs has announced an *Inquiry into the scientific, ethical and regulatory aspects of human cloning*, to review the recommendations of AHEC. The Committee, or the Minister, could request that AHEC undertake a two-stage formal public consultation process on scientific, ethical and regulatory aspects of application of cloning techniques in humans.

The Australian Academy of Science issued, in February 1999, a *Position Statement on Human Cloning:*

> The Academy considers that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited. However, human cells, whether derived from cloning techniques or from ES cell lines should not be precluded from use in approved research activities in cellular and developmental biology.

United Kingdom

The **UK's Human Fertilisation and Embryology (HFE) Act** allows, under a licence from HFEA, research involving human embryos within strict limits which must not exceed the fourteenth day of their development. The HFEA's policy is that it will not license any research which has reproductive cloning as its aim. However, it would consider license applications for other types of research involving embryo splitting or nuclear replacement in eggs, provided that the research falls within one of the purposes of the HFE Act.

The Human Genetics Advisory Committee provides a broad perspective on the implications of genetics and reports to Ministers of the British government, while the Human Fertilisation and Embryology Authority has regulatory responsibility for the Human Fertilisation and Embryology Act, 1990. A working group consisting of both bodies was established to hold a consultation exercise on human cloning and advise government on whether the legislation needs to be strengthened in any specific way. In January 1998, the Human Genetics Advisory Committee (HGAC) and the Human Fertilisation and Embryology Authority (HFEA) issued a consultation document *Cloning Issues in Reproduction, Science and Medicine*.

Following public consultation, the HGAC/HFEA advised, with respect to research using ES cell lines for the cloning of human tissues: *the Secretary of State for Health should consider specifying in regulations two further purposes for which the HFEA might issue licences for research, so that potential benefits can clearly be explored. Firstly, the development of methods of therapy for mitochondrial disease and secondly the development of therapeutic treatments for diseased or damaged tissues or organs.*

Government did not accept this advice but has asked for further expert opinion. A new "Chief Medical Officer's Expert Advisory Group on Therapeutic Cloning" has been established, with terms of reference that include examination of the bases for the HGAC/HFEA recommendations, and examination of alternative methods for tissue repair that have not yet been considered.

The **Royal Society** has issued a statement, *Whither Cloning*, prepared by twelve Fellows and endorsed by the Council of the Royal Society. Council urged that, with respect to research using ES cell lines for the cloning of human tissues, *any modification to existing legislation should be carefully drafted so as not to outlaw the potential benefits that could be derived from research on cloned embryos.*

United States of America

On September 13, President Clinton received from his National Bioethics Advisory Commission (NBAC) its report on *Ethical Issues in Human Stem Cell Research*. President Clinton said:

> Because of the enormous medical potential of such research, I asked the NBAC in November, 1998, to look at the ethical and medical issues surrounding human stem cell research. The scientific results that have emerged in just the past few months already strengthen the basis for my hope that one day, stem cells will be used to replace cardiac muscle cells for people with heart disease, nerve cells for hundreds of thousands of Parkinson's patients, or insulin-producing cells for children who suffer from diabetes.

While NBAC recommended that federal funding should be available for research on donated human embryos surplus to fertility treatments, as well as on primordial germ cells from donated fetal tissue arising from induced abortions. NBAC did not recommend that federal funds should be made available at this time to create human embryos using cloning techniques, but recommended that scientific progress in this area of research should be monitored closely.

Community discussion on the risks and benefits of human ES cell research should be promoted by policy makers and by scientists.

The Australian Academy of Science has supported the Australian Health Ethics Committee in its request that the Minister for Health and Aged Care "should encourage and promote informed community discussion on the potential therapeutic benefits and possible risks of the development of cloning techniques".

It was noted by some Forum participants that scientists are using terms that are not yet understood by the public; community discussion forces clear definition of terminology but can also find new words that are more broadly understood. It was also noted by some Forum participants that broader, social issues should be canvassed during the debate, such as the potential impact on our view of human-kind as medical technology becomes more manipulative, and on attitudes to and by women as potential donors of eggs and embryos for use in tissue repair.

The Academy has been pleased to promote, in a small way, public debate on therapeutic cloning (and the broader issue of human ES cell research), by publication of its *Position Statement On Human Cloning*, by issuing press releases, through information on its Nova website and by hosting the 1999 Forum.

The Academy welcomes, as part of this public information process, the House of Representatives Standing Committee on Legal and Constitutional Affairs *Inquiry into the scientific, ethical, and regulatory aspects of human cloning,* to be chaired by Mr Kevin Andrews, MHR.

The Academy supports the view put forward at the Forum that the NHMRC's Australian Health Ethics Committee might undertake a formal, two-stage, public consultative process into the scientific, ethical, and regulatory aspects of human cloning. This may well arise as a recommendation from the House of Representatives Inquiry and would be a recommendation welcomed by the Australian Academy of Science.

The Australian Academy of Science considers that the NHMRC's Australian Health Ethics Committee might undertake a formal, two-stage consultative process on ethical issues in human embryonic stem cell research.

Glossary

Antigen: Substance (e.g. toxin) that stimulates production of antibodies when introduced into the body.

Blastocyst: a cluster of cells following early cleavage of the fertilised egg, consisting of outer cells that have the potential to form placenta and an inner cell mass with the potential to form an embryo. The first signs of the embryo appear as the primitive streak, about 14 days after fertilisation.

Chromosomes: nucleic acid-protein structure in the nucleus of a cell. Chromosomes carry the heredity factors, genes, and are present in constant numbers in each species. In man, there are 46 in each cell, except in the mature ovum and sperm where the number is halved. A complete set of 23 is inherited from each parent.

Cloning: production of a cell or organism with the same nuclear genome as another cell or organism.

Cytoplasm: the contents of a cell other than the nucleus. Cytoplasm consists of a fluid containing numerous structures e.g. mitochondria that carry out essential cell functions.

Differentiation: an increase in complexity and organisation of cells and tissues during development.

De-differentiation: a decrease in complexity and organisation of cells and tissues.

Undifferentiated: not differentiated.

DNA: Deoxyribonucleic acid, found primarily in the nucleus of cells (some DNA is also found in mitochondria). DNA carries coded information for making all the structures and materials that the body needs to function.

Ectoderm: Outermost layer of embryo in early development.

Egg: the mature female germ cell; also called the **ovum** or **oocyte**.

Embryo: the developing human organism from the time of fertilisation until the main organs have developed, eight weeks after fertilisation. After this time the organism becomes known as a **fetus**.

Embryonic stem (ES) cell line: cultured cells obtained by isolation of inner cell mass cells from blastocysts or by isolation of primordial germ cells from a fetus. ES cells will not give rise to an embryo if placed in the uterus.

Enucleated egg: an egg from which the nucleus has been removed.

Fertilisation: the process whereby male and female gametes unite, beginning when a sperm contacts the outside of the egg and ending with the union of the male and female nuclei in syngamy to form the zygote.

Fetus: the term used for a human embryo after the eighth week of development until birth.

Gene: a hereditary factor composed of DNA. Each of the body's approximately 100,000 genes carries the coded information that permits the cell to make one specific product such as a protein.

Genome: the complete genetic make up of a cell or organism.

Germ cell: a reproductive cell precursor that will eventually give rise to a sperm or ovum. All other body cells are **somatic** cells.

Human reproductive cloning: the production of a human fetus from a single cell by asexual reproduction.

In vitro: in glass; referring to a process or reaction carried out in a test-tube or culture dish.

Mesoderm: middle germ-layer of embryo.

Mitochondria: cellular organelles that provide energy to the cell. The mitochondrion contains genes inherited exclusively from the mother.

Nuclear replacement: a technique which involves placing the nucleus from a diploid cell in an egg from which the nucleus has been removed.

Nucleus (*pl* nuclei): the central protoplasm of the cell that contains the chromosomes.

Oocyte: the mature female germ cell; the egg.

Pluripotent: a cell or embryonic tissue capable of producing more than one type of cell or tissue.

Primordial germ cells: precursor reproductive cells in an embryo or fetus.

Somatic cell: any cell of an embryo, fetus, child or adult not destined to become a sperm or egg cell.

Stem cell: an undifferentiated cell which is a precursor to a number of differentiated (specialised) cell types. Stem cells may be totipotent, pluripotent, or committed to a particular cell lineage (eg neural stem cell).

Telomere: the tip of a chromosome. Loss of telomeres is thought to contribute substantially to ageing.

Telomerase: the enzyme that synthesises telomeric DNA.

Therapeutic cloning: medical and scientific applications of cloning technology which do not result in the production of genetically identical fetuses or babies.

Totipotent: the capacity to give rise to a complete embryo and its placenta.

Transgenic: containing a gene or genes introduced from another individual.

Xenotransplantation: a transplant from one species to another.

Zygote: the single-celled fertilised egg.

Forum attendees, 16 September 1999

(NB: The views expressed in this Forum Summary are those of the Australian Academy of Science and do not necessarily reflect the views of the Forum attendees.)

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