# HUMAN STEM CELL RESEARCH

18 April 2001

The Australian Academy of Science has been pleased to promote public debate on human stem cell research, by publication of a *Position Statement on Human Cloning* (February 1999), by providing information on the Academy's (Nova) web-site and by hosting a Forum on *Therapeutic Cloning for Tissue Repair* (September 1999). During the past twelve months there have been continuing scientific and regulatory developments in the general area of human stem cell research. This paper reviews those recent international developments, reflecting the Academy's on-going support for approved research activities in cellular and developmental biology and the Academy's continuing efforts to contribute to public understanding of the therapeutic potential of stem cell research.

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# PREFACE

In February 1999, the Academy prepared a position statement on human cloning. The Academy's statement distinguished between **reproductive cloning** to produce a human fetus and **therapeutic cloning**, for example, to produce human stem cells.

Therapeutic cloning techniques introduce the possibility of growing self-compatible cells, such as nerve cells for patients with spinal injuries or muscle cells for heart attack victims. The possibility that cellular therapy could one day be a reality is suggested by the combined application of knowledge arising from three significant advances in biomedical research.

These advances are (a) cloning of mammals from adult cells; (b) establishing cultures of human embryonic stem cells; and (c) demonstrating that human fetal nerve stem cells can develop into multiple and appropriate nerve cell types following transplantation (into experimental animals).

These findings provide new opportunities for research in cellular and developmental biology and, taken together, suggest that future possibilities may exist for self-compatible tissue and organ repair.

## The key recommendations in the Academy's Position Statement were

1. *Reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited. However, human cells, whether derived from cloning techniques, from embryonic stem cell lines, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.*
2. *The Minister for Health and Aged Care should encourage informed community debate on therapeutic benefits and risks of development of cloning techniques.*
3. *If Australia is to capitalise on its undoubted strength in medical research, it is important that research in therapeutic cloning should not be inhibited by withholding federal funds or prevented by unduly restrictive legislation.*
4. *It is essential to maintain peer review and public scrutiny of all research involving human embyros and human embryonic stem (ES) cells undertaken in Australia. The Academy recommends that a national regulatory two-tier approval process be adopted for research on human embryos and human ES cells. Approval to undertake any research involving human embryos and human ES cell lines would need to be obtained from a duly-constituted institutional ethics committee prior to further assessment by a national panel of experts, established by the National Health and Medical Research Council. Approval would be based on the scientific merits, safety issues and ethical acceptability of the work.*

The Academy's Position Statement was published on 4 February 1999, shortly after the Australian Health Ethics Committee (AHEC) provided advice to the Minister for Health and Aged Care in a report entitled *Scientific, Ethical and Regulatory Considerations Relevant to the Cloning of Human Beings* on 16 December 1998. The recommendations of AHEC are given in the body of this document. The advice from AHEC, a Committee of the National Health and Medical Research Council, was referred on 12 August 1999 by the Minister for Health and Aged Care to the House of Representatives' Standing Committee on Legal and Constitutional Affairs. The Standing Committee's *Inquiry into the scientific, ethical and regulatory aspects of human cloning* is expected to report by mid-2001. The submission to the House of Representatives' Inquiry from the Australian Academy of Science is given in Appendix 1.

The Academy held a Forum on *Therapeutic Cloning for Tissue Repair* in September 1999 with the objective of contributing to ongoing community discussion on human cell therapies.

## Academy recommendations arising from the September 1999 Forum were

1. ***The Academy supports the view put forward at the Forum that the National Health & Medical Research Council should be asked to encourage research into stem cells obtained from adult organisms.***
2. ***The Academy supports the view put forward at the Forum that regulation within a uniform, national legislative framework can provide the accountability in research that the public demands.***
3. ***The Academy supports the view put forward at the Forum 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.***

During the past twelve months there have been continuing scientific and regulatory developments in the general area of human stem cell research. This paper reviews recent national and international developments, reflecting the Academy's on-going support for approved research activities in cellular and developmental biology and its continuing efforts to contribute to public understanding of the therapeutic potential of stem cell research.

# EXECUTIVE SUMMARY

The science of stem cell therapies has the potential to lead to treatments for major degenerative diseases, such as Alzheimer's disease, Parkinson's disease, heart disease and insulin dependent diabetes, by providing healthy cells to replace diseased tissues and organs. Stem cell therapy may also have application in delivery of healthy genes to organs with a missing or defective protein.

The focus of current research in human stem cells is on human embryonic stem (ES) cells, which have the potential to develop into any mature adult cell, and on scattered adult stem cells which occur in some, but not all, adult tissues. There is some objection to the use of human ES cells in research because the cells are derived from a one-week old human embryo when it is a microscopic hollow mass of about 200 cells.

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, thus making it unnecessary to use ES cells for research into cell therapies.

In practice, our knowledge of many cellular and developmental processes is imperfect. Without an understanding of the molecular and functional properties of factors that control early embryonic cell differentiation, reprogramming of adult cells has serious technical limitations. Adult stem cells cannot adequately substitute for ES cells in basic research concerned with 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.

It is 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. 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; State laws should be reviewed to apply a more consistent application of national standards.

The Academy of Science continues to promote public discussion on human stem cell research. 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. 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. These issues would include the attitudes of society to and about women as potential donors of eggs and embryos for therapeutic cloning.

In light of recent development, the Academy restates its position of opposition to cloning “whole human being” on the basis of safety and general ethical concerns.

The recent developments in stem cell research show the scientific and ultimately therapeutic importance of undertaking basic research in cellular and developmental biology prior to clinical application of that research.

# INTRODUCTION

The recent history of biomedical research and development has been marked by major technological developments which have provided laboratories an abundance of reagents that had previously been very scarce. Monoclonal antibody techniques, that can provide unlimited quantities of exquisitely sensitive antibodies, permitted rapid advances in knowledge in cell biology in the 1970s and led to many applications in diagnostic medicine. Similarly, molecular genetic techniques, that can provide unlimited quantities of genes and their products, permitted extraordinary advances in knowledge of cell biology in the 1980s and 1990s, and have resulted in many applications in therapeutic medicine.

**Human stem cells are no longer a limiting factor in biomedical research**

The most recent technological breakthrough that will stimulate research and development in cell biology in the next decade is refinement of the techniques necessary to isolate and culture human stem cells. Embryonic stem (ES) cells derived from human **blastocysts** (early embryos) not only have the capacity to form the three germ layers that make all the organs in the body, but also the capacity to multiply indefinitely in cell culture. This opens up the possibility that human stem cells, until now a scarce and limiting factor in biomedical research, may be available in adequate quantities to permit rapid advances in knowledge and in new medical applications in stem cell therapy.

Stem cell therapy may take various forms. Limited stem cell therapy is already in use in the form of bone marrow transplantation in some cancer patients. But the idea that cells could be taken from a patient's tissue, then modified in some way to permit transplantation back into that patient to restore damaged organs, was deemed impossible prior to the cloning of the sheep "Dolly" in 1997.[1] Before the cloning experiments, it was widely accepted that cell differentiation was unidirectional and irreversible. It was thought that precursor cells became more and more specialised during development of an organism, through irreversible regulation of gene expression. The sheep "Dolly" was derived from an adult mammary gland cell, showing that a specialised adult cell could be reprogrammed to begin development once again.

The science of stem cell therapies has the potential to lead to treatments for major degenerative diseases, by providing healthy cells to replace diseased tissues and organs.[2] Stem cell therapy may also have application in delivery of healthy genes to organs with a missing or defective protein. This paper provides the current status of stem cell research and stem cell therapies, and considers how this work can proceed within an appropriate legislative and regulatory environment.

Stem cell therapies may be used to treat diseased tissues and organs

# DEVELOPMENTS IN STEM CELL RESEARCH

## Definition of stem cells.

**Stem cells** are precursor cells that branch into multiple types of tissues. There are important distinctions, however, regarding how developmentally plastic these cells are; that is, how many different paths they can follow and to what portion of a functioning organism they can contribute.

**Totipotent stem cells** are cells that can give rise to a whole organism as well as to every cell type of the body. **Pluripotent stem cells** are capable of giving rise to a plurality of tissue types, but not to a functioning organism. **Multipotent stem cells** are more differentiated cells (that is, their possible lineages are less plastic/ more determined) and thus can give rise to a more limited number of multiple tissue types. For example, a specific type of multipotent stem cell called a mesenchymal stem cell produces bone, muscle, cartilage, fat and other connective tissues. A better known example is the capacity of bone marrow stem cells to constantly renew red and white blood cells. Stem cells can generate new cells while maintaining their own numbers.

## Sources of stem cells.

There are several potential sources for stem cells. **Embryonic stem cells** (ES cells) are derived from the inner cell mass of a **blastocyst** (a very early embryo). Human 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. For this reason ES cells are called pluripotent stem cells.

**Human ES cells have the potential to turn into nerve, muscle and blood cells**

Embryonic stem cells were isolated from mice nearly 20 years ago, but isolation and maintenance of human ES cells remained elusive until 1998. Human ES cells have been isolated from one-week old human embryos by scientists at the University of Wisconsin[3] and jointly at the University of Singapore and at Monash University.[4] Techniques have been developed to permit the *in vitro* culture and proliferation of human ES cells, perhaps in perpetuity.

In theory, human ES cells could be obtained through cloning techniques, by replacing the nucleus of an unfertilised egg with the nucleus of an adult somatic cell. Should this be done for the purpose of harvesting ES cells from the inner cell mass of the blastocyst for medical applications, the process would be known as **therapeutic cloning**.

Scattered stem cells in the mature adult are constantly renewing certain parts of the human body, although stem cells have not been found in all adult organs. **Adult stem cells** replenish blood, mend the lining of the gut and renew skin cells. Until recently, these adult stem cells have been considered multipotent stem cells, committed to a particular cell lineage. New research[5] suggests some adult stem cells may be reprogrammed to follow novel cell lineages by a mechanism known as transdifferentiation.

## Embryonic stem cell research.

Mouse ES cells are widely used in medical research to introduce new genes into specialised strains of experimental mice. Ongoing research at the University of Adelaide,[6,7] 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.

**Researchers at the University of Adelaide have found factors that control differentiation and de-differentiation of mouse ES cells**

Non-human primate ES cells[8] were not isolated in rhesus and marmoset monkeys until fifteen years after the first isolation of ES cells in mice. 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 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.[9]

Human ES cells developed in 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.[4] 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.

**The Monash University group has established four human ES cell lines under NIH guidelines**

The Monash University group reported in March 2001[10] that it has established four human ES cell lines, from cells extracted from blastocysts by colleagues in Singapore and derived in compliance with National Institutes of Health guidelines. These cells are available to colleagues under a standard agreement, as are human ES cell lines developed in Wisconsin and now distributed to about 30 institutions in the United States and elsewhere.[11]

## Adult stem cell research.

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.[12]

Our knowledge of these processes is imperfect. Without a keen understanding of the molecular and functional properties of factors that control early embryonic cell differentiation, reprogramming of adult cells has 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; and identification of factors in cytoplasm of the oocyte that rejuvenate the adult nucleus.

**Re-programming of adult cells** may be possible, following reports that human marrow cells behave like nerve cells when injected into the brains of rats.[13] More recently, it has been shown that bone marrow cells can generate new heart muscle cells, in mice with damaged hearts.[14]

**Bone marrow cells can generate new heart cells**

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.[15] 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 this way. One major limitation may be the difficulty in accessing the organ and tissue source, such as the brain, with safety.

Identification of growth factors that would stimulate scattered stem cells to mature in order to produce a variety of human tissues is an ongoing area of research. 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 (egg) that rejuvenate the adult nucleus may one day be used to generate stem cells. 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, which 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.

## Overview

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. There is also a need to understand the potential risk that undifferentiated cells might become cancerous under certain conditions. One technical limitation in genomic reprogramming may be changes in the methylation of genomic DNA.[16]

Alternative approaches to tissue repair that do not involve human embryos, but make use of scattered stem cells in the adult, may one day be a reality

Alternative approaches to tissue repair that do not involve human embryos, but make use of scattered stem cells in the adult, 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.

# POTENTIAL STEM CELL THERAPIES

Therapeutic applications of human ES cell research in tissue repair potentially include therapeutic cloning for tissue repair; a generic ES cell for tissue repair; or 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. These cells would not be rejected by the immune system. 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 blastocyst stage, in order to obtain self-compatible ES cells.

**For therapeutic cloning to succeed, techniques would need to be much more efficient than they are today**

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 is slowly improving, 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 concentrate on producing generic tissue that could be used in treating a multitude of patients. For example, one idea is that genetic engineering techniques may disrupt the so-called transplantation genes that encode proteins

on the surface of the cell and tag them as foreign. Once tagged, cells are subject to an immune attack, so any therapeutic procedures need to take this 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

Immune tolerance may be achieved by placing ES cells in a patient's bone marrow

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. Dr James Thomson (*New York Times*, April 3, 2001) believes that a tissue bank of embryonic stem cells would be unnecessary because immune tolerance could be achieved by placing ES cells in a patient's bone marrow, then transplanting them wherever needed.

## Adult stem cell therapies

There has been much early activity in clinical research involving transplantation of allogeneic (self) haemapoietic stem cells in a range of diseases (metastatic renal cell carcinoma, severe aplastic anemia, acute lymphocytic leukemia, myelofibrosis). There is ongoing work in improving the outcome of transplantation of allogeneic (self) haemapoietic stem cells, by the simultaneous

Stem cells from mouse bone marrow turned into functioning heart muscle cells after being injected into a damaged mouse heart. The study used adult stem cells. The technique will be tried on rhesus monkeys starting in three months time and if successful, clinical trials on people could begin in three years. Bone marrow cells may be an ideal solution to the problem of repairing damaged hearts, as they give rise to both heart muscle and blood cells and can be harvested from the patient to prevent rejection.

The risks of cell therapy remain unknown. *The New England Journal of Medicine* (March 8, 2001)[17] has reported that when fetal substantia nigra cells were transplanted into patients with Parkinson's disease, there was no improvement in older patients but in some younger patients there were serious side-effects. Parkinson's disease occurs when cells of the substantia nigra region in the base of the brain die, for unknown reasons. The hope was that the fetal substantia nigra cells might take over for them.

The risks of cell therapy are unknown

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.

# OVERSIGHT OF RESEARCH ON HUMAN STEM CELLS

## Safety and ethics.

Research on human stem cells should be 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*[18] regulates research conduct in Australia. It is a generic statement and covers all the immediately foreseeable ethical issues that may arise from the medical genomics revolution. It provides detailed directions regarding the composition and functions of Human Research Ethics Committees. It has sections providing guidance in such subjects as genetic research, the use of tissue, clinical trials, multi centre trials, innovative therapy, privacy and intellectual property. 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 inspirational in striving for the highest international standards in research. This statement 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. It applies to all disciplines of research impacting on or involving humans.

With respect to research involving human embryos, the National Code refers to the 1996 NHMRC *Ethical Guidelines on assisted reproductive technology.*[19] 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 the *Ethical Guidelines* (Section 6.4).

> *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 *Ethical Guidelines* (Section 11.1) 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*** (Assisted Reproductive Technologies) ***treatment program.***

At the Academy's Forum on *Therapeutic Cloning for Tissue Repair*, discussants identified a number of criteria for judging the ethical acceptability of various procedures relating to use of human embryos in research. These criteria are applicable whether the embryos were surplus to *in vitro* fertilisation treatments or produced by cloning techniques. They include

- 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 embryonic stem cell research would be defined as an important issue for public debate. Should research in non-primate mammalian species be so successful that reproductive cloning became safe, reliable and cost effective, there might be pressure to reopen the debate on the topic; this, however, appears unlikely in the near future.

## Legislation and regulation.

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.[20]

It is difficult to legislate effectively in an area of rapidly developing technologies

It is difficult to legislate effectively in an area of rapidly developing technologies. This 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.

It is 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. 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.[21]

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.

Regulation within a uniform, national legislative framework can provide the accountability in research that the public demands.

**Legislation should not regulate the details of research practice**

# NATIONAL RESPONSES TO HUMAN STEM CELL RESEARCH

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 Academy are those from countries which have populations with diverse religious views, including Australia, the United Kingdom and the 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 advice from AHEC was referred on 12 August 1999 by the Minister for Health and Aged Care to the House of Representatives' Standing Committee on Legal and Constitutional Affairs. The Standing Committee's *Inquiry into the scientific, ethical and regulatory aspects of human cloning* is expected to report by mid-2001.

In December, 2000, *The Gene Technology Act 2000* was passed, with amendments by the Senate. The Senate amendments to section 192 (regarding human cloning and animal-human chimeras) require clarification through additional regulations. Given the intention to roll back powers to the States, clarity may be obtained in the States' cloning legislation.

## 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.***[22]

Government did not accept this advice but asked for further expert opinion. A new "Chief Medical Officer's Expert Advisory Group on Therapeutic Cloning" was 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 House of Commons (December 2000) and the House of Lords (January 2001) voted in favour of permitting research using human embryonic stem cells and for the first time approved the creation of embryos for specific research purposes. The European Parliament has urged Britain to stop its plans. The European Commission has declared that it will not seek to develop pan-European legislation on the issue, even though the European Parliament has called for an outright ban on development of the technology.

The Royal Society in November 2000,[23] prepared a report on stem cell research and therapeutic cloning. It concluded that it is very unlikely that scientists will be able to answer within the next 10 years all of the outstanding questions about stem cells and it might be several decades before we achieve a full understanding of how the specialised state of cells is achieve and maintained.

> ***But much more basic research is required to find out how stem cells from non-embryonic sources can be extracted, kept alive in the laboratory, multiplied for extended periods of time. And directed to form specific types of specialised cells. The progress of this research would be facilitated by the study of embryonic stem cells.***

## United States of America

In 1999, President Clinton commented on the National Bioethics Advisory Commission (NBAC) report on *Ethical Issues in Human Stem Cell Research*.[24]

> ***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.

Following more consultation, the National Institute of Health (NIH)[25] guidelines for research using human pluripotent stem cells were revised in January 2001 and detail the conditions under which NIH funds can be used to conduct research.

The Bush administration is undecided on whether to allow federal funding of human embryonic stem cell research. The American Academy for the Advancement of Science[26] has written (March 6, 2001) to President Bush, stating:

> ***One of the misconceptions held by some is that study of adult stem cells will be sufficient to realize the medical promise of this line of research. But the prevailing view of expert scientific opinion is that it is far too early to know if adult stem cells have the same potential as embryonic stem cells. It is important to convey to the public the limitations and preliminary nature of much of the research on adult stem cells. It is likely to take years to discover whether adult stem cells will be effective in treating many diseases that may be treatable sooner with embryonic or fetal stem cells.***

# CONCLUSION

The Academy of Science continues to promote public discussion on human stem cell research. 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. 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.

# 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.

**Multipotent stem cells** are differentiated cells (that is, their possible lineages are less plastic/more determined) and thus can give rise to a limited number of multiple tissue types.

**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.

**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).

**Substantia nigra cells:** is an area of the brain rich in dopaminergic neurons (neurons that make the neurotransmitter dopamine).

**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 whole organism.

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

**Xenotransplantation**: a transplant from one species to another.

**Zygote**: the single-celled fertilised egg.

# NOTES


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# APPENDIX 1

*Australian Academy of Science*
*Ian Potter House, Gordon Street, Canberra 2601*

*Professor John W White CMG, FAA, FRS*
*Secretary, Science Policy*
*Tel: 02 6249 3578 Fax: 02 6249 4903*

27 October 1999

Ms C Surtees
Secretary
House of Representatives Standing Committee
on Legal and Constitutional Affairs
Parliament House
Canberra ACT 2600

Dear Ms Surtees,

**Inquiry into scientific, ethical and regulatory aspects of human cloning**

I have pleasure in enclosing a submission from the Academy to the above inquiry. The submission expands on the Academy's position statement and reaffirms our four key recommendations which are provided below.

1. 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, from ES cell lines, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.
2. The Academy strongly supports the recommendation of AHEC 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".
3. If Australia is to capitalise on its undoubted strength in medical research, it is important that research on human therapeutic cloning is not inhibited by withholding federal research funds or prevented by unduly restrictive legislation in some States.
4. It is essential to maintain peer review and public scrutiny of all research involving human embryos and human ES cell lines undertaken in Australia. The Academy supports the view that a national regulatory two-tier approval process be adopted. Approval to undertake any research involving human embryos and human ES cell lines would need to be obtained from a duly-constituted institutional ethics committee (IEC) prior to assessment by a national panel of experts, established by NHMRC, of the scientific merits, safety issues and ethical acceptability of the work.

A summary of the forum held on 16 September is near completion and I will arrange copies to be sent to you as soon as it is available. The Academy looks forward to working with the Committee on this very important undertaking.

Yours sincerely,

John W White

## Submission to the Standing Committee on Legal and Constitutional Affairs

### Inquiry into scientific, ethical and regulatory aspects of human cloning

### *Terms of reference*

**The Committee shall review the report of the Australian Health Ethics Committee of the National Health and Medical Research Council entitled *Scientific, ethical and regulatory considerations relevant to cloning of humans beings* dated 16 December 1998**

The Australian Academy of Science has made public its position on scientific, ethical and regulatory aspects of human cloning, outlined in the enclosed booklet (with glossary) entitled *On Human Cloning: A Position Statement*, published on 4 February, 1999. The Position Statement has the unanimous endorsement of the Council of the Australian Academy of Science. The Academy has made four recommendations regarding application of cloning technology in humans (Annex I).

The Academy, in establishing its position on human cloning, reviewed the report of the Australian Health Ethics Committee (AHEC) of the National Health and Medical Research Council entitled *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings* dated 16 December 1998.

Therefore the Academy is pleased to respond to the House of Representatives Standing Committee on Legal and Constitutional Affairs Inquiry into the scientific, ethical and regulatory aspects of human cloning, that intends to review the AHEC report to the Minister for Health and Aged Care.

The reports of the Academy and of AHEC have several commonalities.

1. The Academy and AHEC agree that it is very important to promote informed community discussion on the risks and benefits that might flow from applications of cloning technologies. For this reason, the Academy welcomes the timely Inquiry by the House of Representatives Standing Committee on Legal and Constitutional Affairs as an opportunity to improve public understanding of this area of medical research.

   Further public debate would be encouraged if the Australian Health Ethics Committee was to undertake a formal, two-stage, public consultative process into the scientific, ethical, and regulatory aspects of embryonic stem cell research.

2. Another point of agreement relates to concerns about reproductive cloning. The Academy makes a distinction between *reproductive cloning* to produce a human fetus and *therapeutic cloning* to produce human stem cells, tissues and organs. The need for this distinction is illustrated by the scientific developments in the past year, many of which were reported at a Forum on *Therapeutic Cloning for Tissue Repair*, hosted by the Academy on September 16, 1999. The Academy considers reproductive cloning to produce human fetuses unethical and unsafe, and recommends that reproductive cloning should be prohibited. AHEC recommends that the Commonwealth Government should reaffirm its support for the UNESCO *Declaration on the Human Genome and Human Rights,* Article 11, which states in part that *practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted.*

3. A third point of agreement between the Academy and AHEC is that cloning technology is an exciting advance in medical research which has the potential to revolutionise treatment of degenerative diseases. As the Academy observed in its publication *On Human Cloning: A Position Statement*:

   Cloning techniques may one day revolutionise medical treatment of damaged tissues and organs, should it become possible to use human adult cells as the starting material for growth of new tissues. At present, one human organ, skin, can be grown in the laboratory to provide self-compatible skin grafts for burns victims. The possibility of growing other self-compatible cells, such as nerve cells for patients with spinal injuries or muscle cells for heart attack victims, could one day be a reality, albeit within an unknown time-frame. That such a possibility could become a reality is suggested by the combined application of knowledge arising from three recent and significant advances in biomedical research.

   These advances are

   (a) the cloning of mammals from adult cells;

   (b) the establishment of cultures of 'all-purpose' cells, human embryonic stem (ES) cells with the potential to grow into many different cell types; and

   (c) the demonstration that human fetal nerve stem cells can develop into multiple and appropriate nerve cell types following transplantation (into experimental animals).

   These findings provide new opportunities for research in cellular and developmental biology and, taken together, suggest that future possibilities may exist for self-compatible tissue and organ repair.

The possibility of partial reversal of differentiation of a person's adult cells to form regenerative stem cell types was mooted at the Forum on *Therapeutic Cloning for Tissue Repair*. The Academy recognises that this is an approach preferred, from certain religious viewpoints, to the complete reprogramming of adult cells using cloning techniques. This route will not be available until a great deal more is known about cell growth factors and their receptors, and, even then, may not be available for all types of tissue repair. Furthermore, research in one of the identified approaches (say, in ES cells) is currently the most obvious way ahead to inform research in other areas, such as in stimulation of dispersed, partially-committed stem cells.

4. Finally, the Academy and AHEC both recognise the need for regulation of research using cloning techniques in humans, so that the public can be assured that only responsible research, properly assessed on its scientific merit, on safety issues and on its ethical acceptability, will be undertaken in Australia.

Despite this general commonality between the Academy's position and the AHEC report, there are some differences with respect to human embryo experimentation and how such research is best regulated. The Academy is of the view that human cells, whether derived from cloning techniques or from embryonic stem (ES) cell lines should not be precluded from use in approved research activities in cellular and developmental biology.

In Australia at present, production of human ES cells would be approved only in exceptional circumstances under National Health and Medical Research Council (NHMRC) *Ethical guidelines*, originally prepared to ensure ethical practices in *in vitro* fertilisation (IVF) clinics. Therapeutic cloning is not permitted. For Australia to participate fully and capture benefits from recent progress in research, it may well be necessary to clarify the 1996 NHMRC *Ethical Guidelines on Assisted Reproductive Technology* and repeal restrictive legislation in some States. This could be done in the context of establishing a national regulatory arrangement, taking into account advances in biomedical research and best practice elsewhere. The regulations should be binding on both publicly and privately-funded research activities. An appropriate two-tiered regulatory model is already in place in Australia, where the Gene Therapy Research Advisory Panel advises and supports Institutional Ethics Committees.

It is essential to maintain peer review and public scrutiny of all research involving human embryos and human ES cell lines undertaken in Australia. The Academy supports the view that a national regulatory two-tier approval process be adopted. Approval to undertake any research involving human embryos and human ES cell lines would need to be obtained from a duly-constituted institutional ethics committee (IEC) prior to assessment by a

national panel of experts, established by NHMRC, on the scientific merits, safety issues and ethical acceptability of the work.

The Academy has recommended in our Position Statement that legislation set limits on research practices, such as prohibiting the cloning of human fetuses, but that details of research practice should be subject to regulation under the law. Regulation of therapeutic cloning research should take account of the rapid development of new technologies and the changing applications of those technologies. A national panel of experts, sensitive to community values and to a changing research environment, should be established. National regulation provides more consistent application of national standards and would ensure greater accountability than individual IECs operating within varying State laws. The need for national oversight of therapeutic cloning, 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.

Several countries have recommended establishment of national regulatory bodies to license and regulate assisted reproductive treatments, including Canada (The Canadian Royal Commission into New Reproductive Technologies, 1989), the United Kingdom (under the Human Fertilisation and Embryology Authority) and the United States (draft report of the National Bioethics Advisory Commission, 1999). In Australia, the regulatory system has worked well in those States without legislation regarding assisted reproduction and embryo research, for both privately and publicly-funded clinics, as well as laboratories, guided by the standards set by the National Health and Medical Research Council. With more than 200 Institutional Ethics Committees active in Australia, there is ample evidence that regulation rather than legislation can provide the transparency and accountability that the public demands.

There is another matter on which the Academy has comment. The AHEC Report suggests the establishment of a primate research facility for a program related to cloning and its associated technologies. The Academy does not support this proposal because primate work is less relevant now than at the time of writing of the AHEC report.

## Annex I

1. 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, from ES cell lines, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.

2. The Academy strongly supports the recommendation of AHEC 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".

3. If Australia is to capitalise on its undoubted strength in medical research, it is important that research on human therapeutic cloning is not inhibited by withholding federal research funds or prevented by unduly restrictive legislation in some States.

4. It is essential to maintain peer review and public scrutiny of all research involving human embryos and human ES cell lines undertaken in Australia. The Academy supports the view that a national regulatory two-tier approval process be adopted. Approval to undertake any research involving human embryos and human ES cell lines would need to be obtained from a duly-constituted institutional ethics committee (IEC) prior to assessment by a national panel of experts, established by NHMRC, of the scientific merits, safety issues and ethical acceptability of the work.