Submission from
THE AUSTRALIAN ACADEMY OF SCIENCE

For consideration by
THE 2010 REVIEWS OF *Prohibition of Human Cloning for Reproduction Act 2002* and *Research Involving Human Embryos Act 2002*

SUMMARY

Since February 1999, the Australian Academy of Science (the Academy) has adopted as its policy the following:

"Human cells, whether derived from cloning techniques, from embryonic stem (ES) cell lines, or from primordial germ cells, should not be precluded from use in approved research activities in cellular and developmental biology." "Reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited."
(Australian Academy of Science (1999) *On Human Cloning: A position statement*)

The two Australian laws that relate to embryo experimentation, which were first adopted by the Commonwealth Parliament and by each State jurisdiction in 2002, and amended in 2006, reflect the position of the Academy. These Acts are currently being reviewed. The Academy argues, as its overarching position, that these laws have served Australia well and do not need revision.

The Acts prohibit human cloning and provide mechanisms that guarantee ethical oversight by properly constituted committees in relation to the creation and use of stem cells derived from a human embryo or by transfer of a somatic cell nucleus to an enucleated oocyte. These provisions have been effective and there is no evidence that demonstrates or suggests that any research has been carried out that is not in strict accordance with the provisions of the Acts.

The Academy believes that current research, particularly in relation to clinical use of stem cells to treat human disease, continues to require the ability to produce and to experiment on human embryonic stem (ES) cells as well as other types of human stem cells, as provided for in the Acts. Since last amended in 2006, a number of licenses to create human ES cell lines have been issued in Australia, and global clinical trials with ES cells have commenced (e.g. for spinal injuries and for eye diseases), as have trials with adult stem cells. There is continuing extensive research and development in the stem cell field but it is not yet clear which type of stem cell will be most useful for each area of clinical practice. The Academy urges the review committee to extend the provisions of the existing Acts without change.

The Academy discusses several issues that have arisen as a result of scientific advances over the past three years, one of which might be dealt with by an amendment to the existing NHMRC regulations.

BACKGROUND

Human stem cell research is a relatively new field in which there is much scientific and medical interest. While experiments on stem cells have been conducted for many years in developmental biology laboratories using animal models, the isolation of human stem cells from a variety of sources that retain pluripotency in culture for long periods provides many new opportunities for basic and clinical research. Stem cells may be derived directly from embryonic or fetal tissue, cord blood, infant or adult tissue, or can be induced from adult cells either by viral transduction of several specific factors (induced pluripotent stem cells) or by somatic cell nuclear transfer into an enucleated oocyte. There is interest in using stem cells to regenerate cells and tissues that do not function properly and cause disease (regenerative medicine).

Human ES cells can only be derived (in Australia) from embryos that have been prepared for *in vitro* fertilisation (IVF) purposes, and are either no longer required by the couple providing the egg and the sperm or are "unfit to transfer" due to the presence of a genetic mutation or abnormality (such as an embryo that has been diagnosed as having the genetic mutation that will cause cystic fibrosis or muscular dystrophy). The embryos used to prepare embryonic stem cells usually have about 100 cells and are the size of a pinhead. Embryonic stem cells grow in culture and can "differentiate" into cells of every kind of tissue: blood, skin, liver and brain. Such embryos will be destroyed if not used for research and are only used if the couple wishes to donate them; preparation of ES cells from such an embryo can only proceed after consent of both donors is obtained and the researchers hold a license issued by the NHMRC Licensing Committee.

Induced (human) pluripotent stem cells (iPS cells) are prepared by altering cells from skin or other tissues biochemically, to "wind them back" to a more primitive stage that in some ways resemble embryonic stem cells. Somatic cell nuclear transfer (SCNT) also creates cells that in some ways resemble embryonic stem cells, by transferring the nucleus from "adult" cells into an egg from which the nuclear DNA has been removed.

Adult stem cells can be prepared from many tissues but such cells usually cannot cross tissue barriers: for example, stem cells from bone marrow can generate multiple types of blood cells, and are therefore very useful for cancer therapy, but they cannot make skin or brain cells.

In general, the younger the tissue from which a stem cell is isolated the more flexible is its developmental capacity. This is why embryonic stem cells are often used as the definitive cell for pluripotency experiments.

STEM CELL RESEARCH IN AUSTRALIA

The Academy has noted in its previous submissions to Government, and in its Symposia, that Australia has a strong tradition of research in stem cell science, building on strengths in immunology, developmental biology, transplantation and IVF. Based on these scientific traditions major infusions of funds to establish the Australian Stem Cell Centre and other stem cell research units were provided through the ARC between 2000 and 2010. Much good research was stimulated by initiatives of the ARC, NHMRC and CSIRO, although other countries (in particular the United States) have recently made a very large investment in stem cell research (in the case of California, $3 billion US) and have succeeded in recruiting scientists from around the world (including from Australia) to their laboratories.

While laboratory research has moved forward vigorously with embryonic, adult and modified stem cells, clinical research has been conducted with more caution. There is a long tradition of bone marrow and cord blood stem cell transplantation in Australia as elsewhere, for the most part directed to improved therapy for leukaemias. However, the first clinical trial of ES cell-based therapy (under appropriate ethical and regulatory supervision) has just begun in the United States (October 11, 2010). Patients with a severe spinal cord injury will be injected with ES cells in order to determine the safety of the procedure (known as a Phase 1 trial, sponsored by Geron Corporation). While the purpose of the trial is to study safety, doctors will also examine the patients for any improvement compared to individuals who receive conventional treatment. Several other trials using ES cells have started since October 2010 or are about to start.

Australia is regarded throughout the world as having an excellent system of regulation of scientific research. There is a national code "The Australian Code for the Responsible Conduct of Research" that is issued by the Australian Government, the NHMRC and the ARC. The scope of the Code includes a note of the legal responsibilities of those conducting research with human subjects, with animals, and with respect to misconduct. The Code is supported by an active network of Human Research Ethics Committees, Animal Experimentation Committees and regulatory agencies (in particular the Therapeutic Goods Administration) that examine the safety of procedures in areas such as recombinant DNA. For embryo research, the final layer of regulation is by the *Prohibition of Human Cloning for Reproduction Act 2002* and *Research Involving Human Embryos Act 2002*, the two Acts that are to be reviewed by your Committee. Surveys have shown that public support is high for both embryonic and adult stem cell research in Australia, provided that it is subject to strict ethical controls and is carried out for medical research and treatment.

Apart from our specific suggestions below, the Australian Academy of Science believes that the Acts are working well and meet the needs of the Australian scientific community within an ethical framework that provides reassurance to the community.

ISSUES ON WHICH THE ACADEMY WISHES TO COMMENT

1. The significance of new research generating iPS cells:

   There has been a great deal of discussion in scientific and lay circles as to the extent to which recent data on generation of patient-specific iPS cells reduces or eliminates the need for stem cells derived from embryos. Some observers, particularly from amongst those who have prior ethical objections to derivation of stem cells from human embryos, have argued that the availability of iPS cells means that cells equivalent to ES cells can be derived in a way that does not pose ethical issues.

   The Academy notes that iPS technology is in a very early phase of development. Papers offering new insights into similarities and differences between iPS cells, ES cells and other stem cells appear in the research literature weekly. The expression profile of iPS cells differs in key respects from the expression profile of genetically identical ES cells[1]. The imprinting (epigenetic modification) of iPS cells differs from that found in ES cells and "adult" cells in culture[2]. This has been confirmed recently by research at

[1] Stadtfeld M, *et al*. (2010) Aberrant silencing of imprinted genes on chromosome 12qF1 in mouse induced pluripotent stem cells. *Nature* 465(7295):175-81.

[2] Doi A, *et al*. (2009) Differential methylation of tissue- and cancer-specific CpG island shores distinguishes human induced pluripotent stem cells, embryonic stem cells and fibroblasts. *Nature Genetics* 41(12):1350-3.

the Salk Institute[3]; the lead author of the study, Professor Joseph Ecker, stated "Embryonic stem cells are considered the gold standard for pluripotency, so we need to know whether – and if so, how – iPS cells differ from ES cells." When discussing this article, and a previous article in Nature by Kim et al[4], the accompanying notes stated "The researchers found that rather than being reset to an embryo-like state, methylation patterns near the tips and centres of chromosomes in the iPS cells resembled those in the adult tissues from which the iPS cells had been derived. This could constrain the types of tissues that the cells are capable of forming."[5] A recent news story in *The Scientist*[6] included the comment that "The research demonstrates that iPS cells are fundamentally different from embryonic stem (ES) cells, and will require much more analysis prior to use in therapies and disease models."

Finally, the therapeutic use of iPS cells has not been proven and they may prove to be more or less safe for this purpose than ES cells and other stem cells. This will become more clear as ES cell clinical trials (for neurological diseases and injury), which are already under way, progress to their conclusion. At the present time, there are no clinical trials involving iPS cells[7]. Any decision as to the relative merits of ES vs iPS cells for any specific clinical application will need to be assessed once such data are available, and not before.

A particularly forceful comment was made recently by the Director of the NIH, Dr Francis Collins (who is well known for his strong espousal of conservative Christian ethical views, as well as the excellence of his scientific research as a human geneticist). Collins stated "… not enough [is] yet known about [iPS] cells to guess whether they have the same therapeutic potential as embryonic stem cells." "Will that matter for the therapeutic uses we all dream of? No one knows, but it would be foolish now to proceed without comparing them at every step to the gold standard for pluripotency – and that remains the human embryonic stem cell. So it's not 'either/or' that we should be pursuing. It's 'both/and'." [8]

Thus, it is the view of the Academy that researchers will continue to need ES cell lines, including the right (under guidelines) to prepare new ES cell lines, for the foreseeable future.

The Academy would apply precisely the same approach to SCNT. It is essential that we retain the capacity to prepare SCNT cells from patients because at this time we do not know whether these cells will be more useful, less useful or the same as those prepared from embryos or using iPS techniques.

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[3] Lister R, *et al*. (2011) Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. *Nature* 471(7336):46-7.

[4] Kim K, *et al*. (2010) Epigenetic memory in induced pluripotent stem cells. *Nature* 467(7313):285-90.

[5] Dolgin E (2011) Flaw in induced-stem-cell model. *Nature* 470(7332):13.

[6] Scudellari, M (2011) The iPSC-ESC gap: Human cells reprogrammed into multipotent stem cells display fundamental differences from true embryonic stem cells. *The Scientist* February 2.

[7] Choi CQ (2010) Cell-Off: Induced pluripotent stem cells fall short of potential found in embryonic version. *Scientific American* February 11.

[8] Boyer PJ (2010) The Covenant. *The New Yorker* (September 6).

Therefore the Academy is firmly of the opinion that scientists in Australia should continue to have the opportunity to generate, and to work with, ES cells from human embryos, to carry out somatic cell nuclear transfer and to generate iPS cells, subject to the ethical provisions embodied in the legislation.

2. Mitochondrial diseases:

   There is, at present, a ban on any experiment that involves placing "three genomes" into an embryo. This restriction is in place because it would be ethically problematic, and lead to community concern, were there to be attempts to "enhance" or manipulate human genomes by introducing genetic material from a third parent. However, this has been interpreted by some as preventing research into new forms of therapy for diseases caused by mutations in the mitochondrial DNA, which is maternally inherited. In this situation, introducing mitochondria from another cell may allow normal development. Recent studies in primates[9] and with human embryos in culture[10] suggest that transfer of the nuclear genes from an embryo into an enucleated donor cell may offer a safe and effective way to prevent inheritance of mitochondrial DNA diseases. (This has been compared to replacing an EverReady battery with a Duracell battery in a children's toy; the mitochondria provide power but no meaningful inherited genetic information.) While this issue only affects a very small number of researchers (and patients), it is an anomaly that should be corrected to allow research with several genomes when the research studies mitochondrial rather than nuclear genomes, provided that only two nuclear genomes are involved. A similar defence, titled *Ethics of Mitochondrial Gene Replacement: From Bench to Bedside*, appeared in the British Medical Journal[11].

   We believe the NHMRC could make changes to the regulations that make it clear that the "three genome" rule applies to nuclear rather than to mitochondrial genomes.

3. Points at which regulation is required:

   Fellows of the Academy, and other noted scientists who work on stem cells, have made representations to us that the current system for ethics approval for the use of existing ES cell lines for new research is excessively bureaucratic, and can result in delays of several months. These representations do not relate to experiments that involve the use of an embryo to make ES cell lines, where it is accepted that rigorous scrutiny (that may take time) is appropriate. However, the current regulations are unclear as to how ES cells that have already been made (perhaps by another laboratory), and are growing in culture, should be treated. If routine experiments with human stem cells are delayed, it is hard for Australian research to be competitive in the international area and will prevent Australian patients receiving early benefits from international advances in regenerative medicine therapies. The Academy argues that full process of deliberation by a Human Research Ethics Committee and the licensing committee should continue to apply when human embryos are used in the experiment but that experiments using human ES cell lines that have been previously prepared using approved protocols

[9] Tachibana M, *et al*. (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells. *Nature* 461(7262):367-72.

[10] Craven L, *et al*. (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature* 465(7294):82-5.

[11] Bredenoord AL and Braude P (2010) Ethics of mitochondrial gene replacement: from bench to bedside. *British Medical Journal* 341:c6021.

should be allowed to proceed according to the usual safeguards laid down in the Code of Practice (and for clinical use by the regulations outlined by the Therapeutic Goods Administration).

The Academy recognises the complexity of the scientific evidence presented in this submission and would welcome the opportunity to present further information in person to the Review Committee, should that be possible.

Secretary for Science Policy Professor BOB WILLIAMSON AO FAA FRS