# *HUMAN PLURIPOTENT STEM CELL RESEARCH: RECOMMENDATIONS FOR CIHR-FUNDED RESEARCH*

***Report of the ad hoc Working Group on Stem Cell Research***

***January 2002***

## TABLE OF CONTENTS

## EXECUTIVE SUMMARY

This report contains the recommendations of the CIHR *ad hoc* Working Group on Stem Cell Research with regard to human pluripotent stem cell research. The Working Group would like to draw attention to the following recommendations (numbering corresponds to the numbering within the main body of the text):

4.1 Research to derive and study human embryonic stem (ES) cell lines or other cell lines of a pluripotent nature from human embryos is eligible for funding provided that:

a) The embryos used were originally created for reproductive purposes and are no longer required for such purposes; **AND**
b) There is free and informed consent from the persons for whom the embryos were originally created for reproductive purposes. Additionally, where "donor" gametes have been used to create the embryos, the gamete providers must have originally given free and informed consent to the unrestricted research use of any embryos created when these embryos were no longer required for reproductive purposes; **AND**
c) Neither the ova nor the sperm from which the embryos were created, nor the embryos themselves, were obtained through commercial transactions, including exchange for service.

4.2 Research to derive and study human embryonic germ (EG) cell lines or other cell lines of a pluripotent nature from human fetal tissue or amniotic fluid is eligible for funding provided that:

a) The proposed research does not compromise the pregnant woman's decision on whether to continue her pregnancy, **AND**
b) There is free and informed consent from the pregnant woman.

4.3 Research to derive and study human stem cell lines of a pluripotent nature from the umbilical cord and placenta is eligible for funding provided that:

a) There is free and informed consent from the mother, or from both parents of the newborn if there are two people committed to parenting. If there is disagreement between the parents, the umbilical cord and placenta cannot be used for research.

4.4 Research to derive and study human stem cell lines of a pluripotent nature from human somatic tissues is eligible for funding provided that:

a) When the tissue is from a legally competent person, there is free and informed consent from the prospective research participant, **OR**
b) When the tissue is from a legally incompetent person, i) the tissue has been obtained from a surgical, diagnostic or other legitimate practice not including research, ii) an appropriate third party has authorized its availability for research, and iii) the donation is in accord with applicable consent law in the province where the donation takes place, **OR**
c) When the tissue is from a cadaver, there is a legally appropriate advance directive that appropriately specifies the use of tissue for stem cell research, or there is authorization from an appropriate third party.

4.5 Research on anonymized human embryonic stem cell lines, embryonic germ cell lines or other cell lines of a pluripotent nature that have been created in Canada, or created elsewhere and imported for research purposes, is eligible for CIHR funding provided that:

a) They were created in accordance with CIHR guidelines.

4.6 Research involving the grafting of human ES cells, EG cells or other human cells of a pluripotent nature into non-human animals (from birth to adulthood) is eligible for CIHR funding, provided that:

a) The research is designed to reconstitute a specific tissue or organ to derive a pre-clinical model, **AND**
b) There is evidence from prior studies in non-human species that the cells are not likely to contribute to gametes, **AND**
c) These non-human animals grafted with human stem cells will not be used for reproductive purposes.

4.7 Research involving the grafting of human stem cells or other human cells of a pluripotent nature into legally competent humans is eligible for CIHR funding provided that:

a) There is overwhelming evidence from pre-clinical models for safety and efficacy, **AND**
b) The research is carried out in well-designed clinical trials, **AND**
c) There is free and informed consent from the prospective research participants.

4.8 Research involving the creation of human embryos by fertilization or parthenogenetic activation specifically to derive stem cell lines or other cell lines of a pluripotent nature is not eligible for funding.

4.9 Research involving somatic cell nuclear transfer into human oocytes for the purposes of developing human embryonic stem cell lines or other cell lines of a pluripotent nature is not eligible for funding.

4.10 Research involving the directed donation of stem cell lines or other cell lines of a pluripotent nature to particular individuals is not eligible for funding, unless the research involves autologous donation.

4.11 Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are combined with a human embryo is not eligible for CIHR funding.

4.12 Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are grafted to a human fetus is not eligible for CIHR funding.

4.13 Research in which human ES cells, EG cells or other cells of a pluripotent nature are combined with a non-human embryo is not eligible for CIHR funding.

4.14 Research in which human ES cells, EG cells or other cells of a pluripotent nature are grafted to a non-human fetus is not eligible for funding.

8.1 CIHR should immediately establish a National Stem Cell Oversight Committee to ensure that human stem cell research eligible for CIHR funding can be reviewed in a timely fashion.

9.1b CIHR should immediately establish an electronically accessible National registry of human embryonic stem cell lines generated in Canada. It should require that all lines generated using CIHR funds be listed with the registry and be made available to other academic Canadian researchers subject to reasonable cost-recovery charges. Participation in the registry should be a prerequisite for obtaining CIHR funding.

9.3 CIHR should form a new group to study the scientific and ethical issues of inter-specific chimeras.

9.4 CIHR should review the field of human stem cell research on an ongoing basis:
a) To redraft the relevant guidelines and, as appropriate, to broaden or narrow the scope of permitted research; and
b) To review the need for national research ethics review and, as appropriate, to amend the review process.

## 1. MANDATE OF THE CIHR

The Canadian Institutes of Health Research (CIHR) was established by the Government of Canada in 2000 to be the funding agency for health research in Canada. The CIHR funds a broad spectrum of health research, including biomedical research, clinical science research, health systems and services research, and population health research.

The CIHR has a duty to ensure that research carried out under its auspices, involving humans or human biological material, meets the highest ethical standards. In general terms the ethical principles governing research involving humans including tissues, biological fluids, embryos and fetuses are laid out in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*. The TCPS applies to all research funded by CIHR and all research conducted at institutions that receive any CIHR funding.

## 2. MANDATE OF THE CIHR *AD HOC* WORKING GROUP

In 1998, scientists succeeded in deriving cell lines from early human embryos and fetuses that could grow and divide indefinitely in the petri dish as unspecialized cells but that could also develop into many specialized cell types, like blood, muscle and nerve, when stimulated in various ways. The combination of unlimited cell proliferation with extensive capacity for making different cell types in culture marked these cells as

pluripotent embryonic stem (ES) or embryonic germ (EG) cells. Their wide differentiative capacity opened up the possibility that they could be used to repair tissue damage resulting from many different human diseases, such as Parkinson's Disease, diabetes, congestive heart failure, and Alzheimer's Disease. At the same time as human ES and EG cells were being characterized, there was a burst of discoveries on the properties of stem cells derived from individual tissues in the adult, which suggested that it might be possible to redirect their differentiation into different pathways. Both embryonic and adult stem cell research are now at an exciting phase where future potential is great, but where the full potential of the different systems are not yet clear. Stem cell research, particularly on human ES cells, has raised a number of ethical concerns, related to both the source and potential use of the cells and has been the subject of much public debate in the media in Canada and worldwide.

Given the research potential and the ethical concerns, the CIHR took a proactive step by convening an *ad hoc* Working Group on stem cell research, consisting of scientists, clinicians, philosophers and a lawyer, with national and international expertise in human reproductive technologies and stem cell research. The charge to the Working Group was to provide guidance to CIHR as to whether human ES or EG cell research should be considered eligible for CIHR funding, in the light of existing guidelines for human embryo research in Canada and the evolving international situation. Research on human adult stem cells was not included in the mandate of the Working Group. However, recent scientific research has raised the possibility of isolating stem cells with properties similar to the pluripotent ES cells from adult tissues. Although the source of adult stem cells does not raise unique ethical concerns, ethical issues about the experimental use of pluripotent stem cells would apply to such cells whether derived from the embryo or the adult. Thus the Working Group considered its mandate to cover all human pluripotent cells, whatever their source and the final recommendations are worded with that consideration in mind.

The Working Group did not reconsider the range of ethical issues such as those relating to the moral status of the human embryo and the commodification of human life, that had been considered previously (and in depth) in the 1993 report of the Royal Commission on New Reproductive Technologies. Rather, the Working Group accepted the findings of the Commission and the subsequent TCPS as the general ethical framework for its discussions. The Working Group first met in November 2000, developed its broad working principles and began its deliberations. The Working Group determined that input from a wide range of stakeholders was important and so a three-month consultation period was initiated following the publication of a Discussion Paper on March 29th. During this period, Health Canada published a draft proposal for legislation on assisted human reproduction (AHR; htttp:// www.hc-sc.gc.ca/english/reproduction/). A review of the draft legislation by the House of Commons Standing Committee on Health was completed on December 12th 2001. The legislation as drafted would regulate all research and clinical use of *in vitro* human embryos created but not used for assisted human reproduction, in both the public and private sector. Also, in the time between the end of the Working Group's consultation period and the publication of this final report, the Bush administration in the U.S. decided to allow federal funding for human embryonic stem cell research using only human ES cell lines existing prior to 9 P.M. on August 9th 2001.

The Working Group has met by teleconference and in person and corresponded by e-mail to assess the responses to the Discussion Paper and the impact of legislative efforts here and in other countries. This final report provides clear recommendations on areas of stem cell research eligible or ineligible for CIHR funding. It also provides more detailed guidelines on issues of informed consent, privacy and confidentiality, and commercialization to assist researchers, CIHR peer-review panels, local Research Ethics Boards (REBs), and a proposed National Stem Cell Oversight Committee in assessing the merits of research proposals. The final recommendations are consistent with the TCPS and largely in line with the draft AHR proposals. They also cover areas such as the derivation and use of pluripotent stem cells from fetal and adult tissues that are outside of the remit of the draft legislation. The Working Group also provides some further general recommendations to both CIHR and the government, relating to oversight and regulation of human stem cell research.

## 3. THE SCIENCE OF STEM CELLS

Stem cells have a unique characteristic that distinguishes them from all other cell types derived from mammalian tissue: they have the ability to divide while maintaining their stem cell identity ("self-renewal"), and, in response to certain stimuli, they can differentiate to form more specialized cells.

Stem cells are found at different stages of development in a wide range of tissues. Stem cells isolated from embryos at the earliest stages of development can be used to derive stem cell lines capable of indefinite growth in the laboratory and with the potential to produce all types of specialized cells. If these cell lines were capable of forming a new fetus and its associated membranes, they would be called "totipotent". To date no such totipotent stem cell lines exist. If the stem cell lines are capable of forming all specialized tissues but not a complete organism, they are said to be "pluripotent."

Pluripotent stem cells can be derived from the inner cell mass of the blastocyst and from the cells in the fetal gonad that would give rise to eggs and sperm. Stem cells of a pluripotent nature capable of forming multiple cell types also occur in fetal or adult organisms in tissues such as bone marrow, skin, and muscle. For a long time, adult stem cells were considered to be restricted to producing specific cell lineages, namely those from the tissue in which the stem cell resides. This conclusion has been challenged recently by some unexpected findings. For instance, stem cells from bone marrow may give rise not only to blood cells but also to muscle, liver and nerve-like cells. Stem cells from the nervous system can give rise to blood and other cell types. These recent findings are exciting and provide new insight into the plasticity of adult stem cells. They have also contributed to the ethical debate about the potential sources of human stem cells. It is not yet clear whether adult stem cells can match the potential and self-renewal capacity of embryonic stem cells. In particular, it has proven difficult to expand populations of adult stem cells in culture for many generations, as can be achieved fairly readily with ES and EG cells.

Scientists have been working with pluripotent ES cells derived from mouse embryos for over 20 years. Their studies have contributed much to learning about mammalian development, as well as to understanding the biological roles of specific genes, through the creation of mice engineered to have alterations in those genes. A major scientific breakthrough occurred in 1998, when laboratories in the U.S. derived pluripotent stem cell lines from human embryonic and fetal tissue. This advance opened the possibility of studying human development and identifying the factors that direct cell specialization. It also opened the way to developing better methods for evaluating drugs for efficacy and safety in a human model rather than in an animal one. Perhaps even more significantly, it opened the way to the possibility of cell therapy, in which stem cells could be grown in the laboratory and used to repair tissues that have degenerated or been destroyed. Pluripotent stem cells stimulated to produce a myriad of different specialized cell types could, in theory, be used to replace tissues destroyed by diabetes, heart disease, Alzheimer's disease, Parkinson's disease, retinal degeneration, muscular dystrophy, spinal cord injury, and so on, without the need for transplanted organs. Successful cell therapy could revolutionize the treatment of a wide range of injuries and degenerative diseases, and thereby make a significant impact on the health care of Canadians.

In order for this promise to be realized, scientists need to know more about the biological signals that direct differentiation, and methods must be found for growing large numbers of the desired type of cells. This will take time and will require the use of a wide range of different stem cell types, including proven pluripotent embryonic, fetal and adult stem cells. At this stage, stem cell research is at the exploratory stage. It is not possible to predict whether pluripotent stem cells derived from embryos or fetuses will be directly useful for therapy or whether the more-readily available stem cells from adult tissues will prove effective. However, it is clear that research on understanding the special properties of ES and EG cells will be vital for progress in translating stem cell research into therapy. Understanding how to control the differentiation of pluripotent embryonic stem cells can lead to techniques to redirect adult stem cells into different pathways. Understanding the unlimited proliferative capacity of embryonic stem cells should provide ways of promoting the proliferation of adult stem cells.

Testing the potential of stem cells can best be achieved by grafting stem cells to the adult, fetus or embryo, either within or between species. The resulting entities, which contain cells derived from two different organisms, are known as chimeras. Research involving grafting of stem cells to the early embryonic environment (the blastocyst or early morula stage), provides the most rigorous test of pluripotency. Mouse ES cells, when transferred into a mouse blastocyst, can contribute extensively to all tissues in the resulting mouse, including the gametes, and can actually generate an entire mouse provided that the placenta is contributed by the host blastocyst. The same kinds of experiments can be performed using tissue-specific adult stem cells and have demonstrated the broad developmental potential of such cells in some instances, e.g. mouse neural stem cells have been reported to produce a variety of tissue types after injection into the mouse blastocyst. Research involving the grafting of animal stem cells into tissues of the animal fetus, either inside the uterus or in culture, allows a narrower range of potential

contributions because of the temporally and spatially restricted location of the introduced cells. However, this approach is very useful for determining whether stem cells can contribute to the development of specific organs and could be useful in assessing the potential of human stem cells in the same way. Research involving the grafting of human stem cells into adult animals is used to test the potential of stem cells for tissue regeneration and provides critical models for future stem cell therapy in humans. Experiments of this sort with tissue-restricted stem cells, such as introduction of human hematopoietic stem cells into immunocompromised adult mice, have been carried out for some time and have provided very important experimental models for studying human disease. The use of a wider range of human stem cells in such adult grafting models will be essential to assess the possible therapeutic potential of these cells.

Some of the types of experiments that are used to assess the potential of mouse stem cells would not be ethical in humans. For example, there is a clear consensus worldwide that it is ethically unacceptable to introduce human ES cells, or other human cell lines known to be pluripotent, into the human blastocyst with the intention of returning the embryo to the uterus to complete gestation (human to human chimeras). Similarly, all experiments in which non-human ES, EG cells or other stem cell lines are introduced into early human embryos and returned to the human uterus are unacceptable (non-human to human chimeras). Short-term experiments of this sort with human embryos in culture also raise serious ethical concerns.

Introduction of human ES, EG or other pluripotent stem cells into non-human embryos and transfer to the non-human uterus also raises concerns because of the possibility of major contributions of the human cells to the somatic tissues and possibly gametes of the resultant (human to non-human) chimera. This applies not only to cell lines, such as ES and EG cells, for which there is good evidence of pluripotency, but also to any human stem cell line, including adult-derived stem cell lines, for which there is evidence that the equivalent non-human cells can make major and widespread tissue contributions in embryo chimeras. Short-term experiments involving such chimerass may be justified in order to fully assess the safe use of the stem cells in later therapy. This issue has not been addressed in detail in any documents on stem cell research to date and is beyond the scope of this document.

## 4. CIHR FUNDING OF HUMAN PLURIPOTENT STEM CELL RESEARCH IN CANADA

The following recommendations of the Working Group build on and extend the findings of the Discussion Paper, taking into account, where appropriate, the feedback received. The recommendations are based on the principles laid down in the TCPS. The TCPS is a document that applies generally to all research involving humans and human biological material. However, it was written prior to the derivation of pluripotent stem cells from human embryos and fetuses. The recommendations that follow help clarify how the ethical principles and articles of the TCPS apply to derivation and use of human embryonic stem cell lines and other human cells or cell lines of a pluripotent nature. In

the recommendations that follow, the **bold** text refers to Articles or text pages of the TCPS.

***Research eligible for CIHR funding***

4.1 Research to derive and study human embryonic stem cell lines or other cell lines of a pluripotent nature from human embryos is eligible for funding provided that:
   a) The embryos used were originally created for reproductive purposes and are no longer required for such purposes (**Article 9.4** states that "It is not ethically acceptable to create human embryos specifically for research purposes"), **AND**
   b) There is free and informed consent from the persons for whom the embryos were originally created for reproductive purposes. Additionally, where "donor" gametes have been used to create the embryos, the gamete providers must have originally given free and informed consent to the unrestricted research use of any embryos created when these embryos were no longer required for reproductive purposes (**Article 9.4 (a) and Article 9.1**); **AND**
   c) Neither the ova nor the sperm from which the embryos were created, nor the embryos themselves, were obtained through commercial transactions, including exchange for service **(Article 9.2)**.

4.2 Research to derive and study human embryonic germ cell lines, or other cell lines of a pluripotent nature from human fetal tissue or amniotic fluid is eligible for funding provided that:
   a) The proposed research does not compromise the pregnant woman's decision on whether to continue her pregnancy (**page 9.4**), **AND**
   b) There is free and informed consent from the pregnant woman (**page 9.4**).

4.3 Research to derive and study human stem cell lines of a pluripotent nature from the umbilical cord and placenta is eligible for funding provided that:
   a) There is free and informed consent from the mother, or from both parents of the newborn if there are two people committed to parenting. If there is disagreement between the parents, the umbilical cord and placenta cannot be used for research.

4.4 Research to derive and study human stem cell lines of a pluripotent nature from human somatic tissues is eligible for funding provided that:
   a) When the tissue is from a legally competent person, there is free and informed consent from the prospective research participant, **OR**
   b) When the tissue is from a legally incompetent person, i) the tissue has been obtained from a surgical, diagnostic or other legitimate practice not including research, ii) an appropriate third party has authorized its availability for research, and iii) the donation is in accord with applicable consent law in the province where the donation takes place, **OR**
   c) When the tissue is from a cadaver, there is a legally appropriate advance directive that appropriately specifies the use of tissue for stem cell research, or there is authorization from an appropriate third party (**page 10.2**).

4.5 Research on anonymized human embryonic stem cell lines, embryonic germ cell lines or other cell lines of a pluripotent nature that have been created in Canada, or created elsewhere and imported for research purposes, is eligible for CIHR funding provided that:

a) They were created in accordance with CIHR guidelines.

It is incumbent on the recipient of the cell lines to ensure that they were derived in a manner consistent with the CIHR guidelines. The recipient must provide satisfactory evidence to the local REB and the proposed National Stem Cell Oversight Committee (see later) that the cell lines fulfill the informed consent provisions before research can begin.

4.6 Research involving the grafting of human ES cells, EG cells or other human cells of a pluripotent nature into non-human adults is eligible for CIHR funding, provided that:

a) The research is designed to reconstitute a specific tissue or organ to derive a pre-clinical model, **AND**
b) There is evidence from prior studies in non-human species that the cells are not likely to contribute to gametes, **AND**
c) These non-human animals grafted with human stem cells will not be used for reproductive purposes.

4.7 Research involving the grafting of human stem cells or other human cells of a pluripotent nature into legally competent humans is eligible for CIHR funding provided that:

a) There is overwhelming evidence from pre-clinical models for safety and efficacy, **AND**
b) The research is carried out in well-designed clinical trials, **AND**
c) There is free and informed consent from the prospective research participants.

***Research ineligible for CIHR funding***

4.8 Research involving the creation of human embryos by fertilization or parthenogenetic activation specifically to derive stem cell lines or other cell lines of a pluripotent nature is not eligible for funding (**Article 9.4**).

4.9 Research involving somatic cell nuclear transfer into human oocytes for the purposes of developing human embryonic stem cell lines or other cell lines of a pluripotent nature is not eligible for funding (**Article 9.5**).

4.10 Research involving the directed donation of stem cell lines or other human cells or cell lines of a pluripotent nature to particular individuals is not eligible for funding, unless the research involves autologous donation.

4.11 Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are combined with a human embryo is not eligible for CIHR funding.

4.12 Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are grafted to a human fetus is not eligible for CIHR funding.

4.13 Research in which human ES cells, EG cells or other cells of a pluripotent nature are combined with a non-human embryo is not eligible for CIHR funding.

4.14 Research in which human ES cells, EG cells or other cells of a pluripotent nature are grafted to a non-human fetus is not eligible for funding.

*Detailed guidelines for application of above provisions:*

## 5. FREE AND INFORMED CONSENT

Timing of free and informed consent

With several categories of human pluripotent stem cell research, there is particular concern regarding the timing of the informed choice process. In these cases, the following provisions must apply.

5.1 Embryos no longer wanted for reproductive purposes may be donated to another couple, used for research (including research to derive and study human ES cells), or discarded. These options should be discussed with the gamete providers (and the embryo providers if these are different individuals), and a decision regarding the eventual disposition of unwanted embryos should be made prior to the collection of gametes and the creation of embryos for reproductive purposes.

5.2 At the time when the embryos are to be used for research to derive and study ES cells and other human cells or cell lines of a pluripotent nature, consent of the embryo providers should be confirmed. A renewal of the consent given by the gamete providers (if the gamete providers are not the same individuals as the embryo providers), is not required provided that appropriate consent for the unrestricted research use of the embryos was given at the time of gamete "donation".

5.3 For research to derive and study EG cells and other human cells or cell lines of a pluripotent nature from human fetal tissue, the option of using fetal tissue for research must only be discussed with the pregnant woman after a free and informed choice has been made to have a therapeutic abortion. A woman's decision about whether to continue her pregnancy must not in any way be influenced by the possible research use of the fetal material.

Disclosure requirements

**Article 2.4** stipulates that "researchers shall provide, to prospective subjects or authorized third parties, full and frank disclosure of all information relevant to free and informed consent."

5.4 For the purpose of obtaining free and informed consent to human stem cell research, at a minimum, researchers shall provide prospective research participants or authorized third parties with the following information.

a) A description of the purpose of the research;
b) A description of the research procedures;
c) A description of reasonably foreseeable harms and benefits that may arise from research participation;
d) An explanation that consent to, or refusal of, research participation will not affect access to treatment;
e) An explanation of the potential uses of the stem cells including any commercial uses, and the presence of any apparent or actual or potential conflict of interest on the part of researchers, their institutions or sponsors;
f) An explanation that the research participants will not benefit directly financially from any future commercialization of cell lines; nor will there be any personal benefit in terms of dispositional authority over any cell lines created (i.e., there will be no directed donation of the cells or cell lines to particular individuals), except if the research involves autologous donation;
g) An explanation that the cell line(s) will be anonymized, except if the research involves autologous donation (see also section 6 below);
h) An explanation that the research could result in the production of a cell line that could be maintained for many years and used for different research purposes;
i) An assurance that prospective research participants are free not to participate and have the right to withdraw at any time before an anonymized cell line is created.

In the case of stem cell research involving human embryos where "donor" gametes have been used to create the embryos, only a subset of the disclosure requirements will apply because consent will be sought for unrestricted research use.

Voluntariness

**Article 2.2** stipulates that "free and informed consent must be voluntarily given, without manipulation, undue influence or coercion." In addition, consent may " … be withdrawn at any time."

5.5 To help ensure voluntariness and to minimize the risk that women and couples will be pressured to create more embryos than needed for reproductive purposes, the physician responsible for the fertility treatment and the person seeking a consent to the disposition of embryos no longer wanted for reproductive purposes (including the option of embryo research) may not be part of the stem cell research team.

5.6 To help ensure voluntariness, at the time the embryo(s) are to be used for research, a reconfirmation of the original consent to the research use of embryos must be obtained from the embryo providers. This requirement affirms the right to withdraw and is necessary because of the possible lengthy delay between the time at which the original consent is given and the time at which the embryos are utilized for research purposes.

5.7 Consent to the research use of embryos is always revocable by the embryo providers who may change their mind regarding the future research use of embryos no longer wanted for reproductive purposes. Gamete providers who consent to the possible future research use of embryos created using their gametes cannot later withdraw their consent. They should be so advised during the informed choice process.

5.8 Researchers should never pressure members of the fertility treatment team to generate more embryos than necessary for the optimum chance of reproductive success; this is tantamount to creating embryos for research.

5.9 To help ensure voluntariness and to minimize the risk that pregnant women will be pressured to terminate their pregnancy to provide fetal tissue for research purposes, the physician responsible for the therapeutic abortion may not be part of the stem cell research team.

5.10 Consent to the research use of unwanted embryos, aborted fetal tissue, umbilical cord or adult tissues should never be a condition, explicit or implicit, of access to treatment.

5.11 Consent to research use of any tissue for stem cell research is always revocable until such time as an anonymized stem cell line has been created.

## 6. PRIVACY AND CONFIDENTIALITY

As with all research involving human tissue and health records, it is important to respect privacy and confidentiality (**Sections 2 and 10**).

6.1 All human stem cell lines, other human cells or cell lines of a pluripotent nature from human embryos, fetuses or adults, must be anonymized (i.e. no personal identifiers), except if the research involves autologous donation.

6.2 All researchers who make stem cell lines available to other academics (as per requirements in Article 7.2 below), will ensure that the lines are anonymized.

## 7. COMMERCIAL ISSUES

7.1 **Article 9.2** stipulates that "in research, it is not ethical to use ova or sperm that have been obtained through commercial transactions, including fee for service." Although the TCPS does not mention commercial transactions involving human embryos, it is clear that there should be no direct or indirect payment for embryos used in research. The same limitation applies to other tissues collected for stem cell research. Financial incentives (including exchange for service) should not be offered to prospective research participants or authorized third parties.

7.2 Subject to reasonable cost recovery charges, human pluripotent stem cell lines produced by researchers who receive any CIHR funding should be made available to all academic Canadian researchers.

7.3 **Article 4.1** stipulates that "researchers … shall disclose actual, perceived or potential conflicts of interest to the REB." For example, if a researcher or his/her institution has any financial interest in the outcome of the research, this should be disclosed to the proposed National Stem Cell Oversight Committee, the REB and the prospective research participants. It should be noted that in some instances, disclosure may not be a sufficient response to concerns about actual, perceived or potential conflicts of interest.

7.4 According to **Article 7.3**, "REBs shall examine the budgets of clinical trials to assure that ethical duties concerning conflict of interest are respected." In research involving human stem cell lines, the same standard should apply. In particular,

a) Copies of contracts between researchers, institutions and industry sponsors and any relevant budgetary information should be provided to the National Stem Cell Oversight Committee and the local REB, to examine and evaluate any potential or actual conflict of interest and to ensure the right to publish freely after a modest interval.

## 8. RESEARCH ETHICS REVIEW

Because of the complex ethical issues and the public concern in this area, it is essential that there be a mechanism to provide a nationally consistent review process for all proposals involving human pluripotent stem cell research. The Working Group makes the following recommendations:

8.1 CIHR should immediately set up a National Stem Cell Oversight Committee responsible for the ethics review of human pluripotent stem cell research, with special emphasis on research involving the derivation of cell lines from human embryos or fetuses. The National Stem Cell Oversight Committee will provide ethical review of research proposals approved by scientific review panels of CIHR, to ensure that research meets CIHR stem cell guidelines. The National Stem Cell Oversight Committee will:

a) Provide a greater degree of accountability than currently exists with the local research ethics review system and thereby foster public confidence;
b) Ensure greater access to appropriate experts with the background and knowledge to review the research;
c) Minimize the potential for conflict of interest, as the reviewers can be completely at arms-length from the research proposals; and
d) Set the stage for a truly national review system that can be implemented as part of the AHR legislation and apply to both private and public sector research.

8.2 Research proposals should first be reviewed by the scientific peer review panels of CIHR. Research proposals approved in principle for funding should then be forwarded to the National Stem Cell Oversight Committee for ethics review, prior to ethics review by the local REB (and Animal Care Committee [ACC], if appropriate). No human pluripotent stem cell research should be funded without both National Stem Cell Oversight Committee and local REB approval.

8.3 Researchers who wish to undertake human pluripotent stem cell research using existing CIHR grants, must submit their new protocols to both the National Stem Cell Oversight Committee and the local REB.

.

8.4 To ensure that the additional ethics review by the National Stem Cell Oversight Committee does not impose unnecessary delays on initiation of research projects, the Committee meetings should be scheduled within one month of the announcement of successful grant applications by the peer review panels.

8.5 In addition to the ethics review responsibilities for grant applications submitted to CIHR, the National Stem Cell Oversight Committee will:

a) Provide ethical review of stem cell research proposals submitted by other public or private granting agencies, if requested;
b) Provide advice on the application of the CIHR stem cell guidelines to investigators, local REBs and ACCs;
c) Provide advice to CIHR, Health Canada, the media and the public about the ethical and scientific issues of human stem cell research in Canada;
d) Develop a system for monitoring ongoing research, compliance with the guidelines, and ensuring that any major changes to ongoing research protocols are reported to the National Stem Cell Oversight Committee;
e) Provide ongoing review and revision of the guidelines in light of changing scientific data and social climate.

8.6 The National Stem Cell Oversight Committee should include members of the general public in addition to members with expertise in the areas of stem cell biology and therapeutics, medicine and health care, ethics, law, and social sciences.

## 9. RECOMMENDATIONS TO CIHR

9.1 CIHR should officially adopt the recommendations proposed by the *ad hoc* Working Group on Stem Cell Research with as little delay as possible.

Following this:

a) CIHR should immediately establish a National Stem Cell Oversight Committee to ensure that human stem cell research eligible for CIHR funding can be reviewed in a timely fashion.
b) CIHR should immediately establish an electronically accessible National registry of human embryonic stem cell lines generated in Canada. It should require that all lines generated using CIHR funds be listed with the registry and made available to other academic Canadian researchers subject to reasonable cost-recovery charges. Participation in the registry should be a prerequisite for obtaining CIHR funding.

9.2 CIHR should collaborate with the other Federal funding agencies to ensure that *The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* is revised (particularly sections 9 and 10) to clarify the ethical guidelines for human stem cell research.

9.3 CIHR should form a new working group to examine the scientific and ethical issues of inter-specific chimeras.

9.4 CIHR should review the field of human stem cell research on an ongoing basis:

a) To redraft the relevant guidelines and, as appropriate, to broaden or narrow the scope of permitted research; and
b) To review the need for national research ethics review and, as appropriate, to amend the review process.

## 10. RECOMMENDATIONS TO HEALTH CANADA

10.1 Health Canada should establish a National Research Ethics Review Committee responsible for the review of certain categories of research, including novel and contentious areas of research, multicentre trials, and large population-based studies that involve international collaborations. The Committee should review such research in both the public and private sectors, so that all researchers are subject to the same oversight. A subcommittee of this National Review Committee could function to review embryonic and fetal stem cell research, and eventually replace the CIHR National Stem Cell Oversight Committee.

10.2 Among the responsibilities of the National Research Ethics Review Committee set up under federal legislation should be examination (along with the local REB) of all industry/researcher/institution contracts for any potential or actual conflict of interest.

10.3 Health Canada should consult members of the CIHR *ad hoc* Working Group on Stem Cell Research in the development of federal regulations regarding stem cell research.

10.4Health Canada should consult relevant stakeholders in the development of a National Research Ethics Review Committee.

Appendix i)

## GLOSSARY

**Blastocyst**: A preimplantation embryo of 30-150 cells. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).
**Chimera**: An organism composed of cells derived from at least two genetically different zygotes, from the same or different species. Chimerism can be produced experimentally at different stages of development, from embryo through to adult.
**Chromosomes**: The structures within the nucleus that consist mostly of DNA and determine the genetic makeup of the organisms. Chromosomes contain genes, working subunits of DNA that carry the genetic code for specific proteins, interspersed with large amounts of DNA of unknown function. A normal human body cell contains 46 chromosomes, half of which are contributed by the father and half by the mother.
**Cloning**: Generation of an embryo by somatic cell nuclear transfer (see below)

> "**Therapeutic cloning**": Sometimes used to refer to cloning of an embryo for the purpose of deriving pluripotent stem cells for therapeutic application.
> "**Reproductive cloning**": Sometimes used to refer to cloning of an embryo for transplantation into a uterus with the intent of producing offspring genetically identical to the nuclear donor.

**Differentiation**: The process by which cells acquire new characteristics and form more specialized cell types.
**DNA:** Deoxyribose nucleic acid; the genetic material of the chromosomes.
**Embryo**: An organism in the early stages of development; in humans, up to about 6 weeks of development.
**Embryo provider**: A couple (occasionally an individual) having custody of an embryo and the authority to make decisions regarding its disposition; not always the biological parent(s) of the embryo.
**Fetus**: An organism from the end of the embryonic period ( 6 weeks of development in the human), up to birth.
**Gamete**: The sex cell (sperm or egg). The functional, mature, male gamete is called a **sperm** while the female gamete is called the **ovum**, or egg.
**Gamete provider**: A person who is a biological parent of the embryo, but does not necessarily have custody of the embryo or any authority to make decisions regarding its disposition.
**Gonad**: An organ that produces sex cells (a testis or an ovary)
**Hematopoietic**: Related to the formation of blood cells, a process that occurs mainly in the bone marrow.
***In vitro* fertilization (IVF)**: Fertilization of an egg by a sperm outside a woman's body.
**Morula:** The stage of the embryo just prior to the blastocyst which consists of a ball of unspecialized cells.
**Neural:** Related to the cells of the nervous system.
**Nucleus:** The portion of the cell enclosing the genetic material of the chromosomes.
**Oocyte**: An immature ovum (egg).
**Ovum**: See "gamete".

**Somatic cells**: The cells of an organism, other than those cells whose descendants may include gametes.
**Somatic cell nuclear transfer** (nuclear transfer, nuclear replacement: see 'cloning'): The transfer of a nucleus from a somatic cell into an unfertilized egg (oocyte) which has had its nucleus removed (i.e. has been 'enucleated').
**Sperm**: See "gamete".
**Zygote**: A fertilized egg formed as a result of the union of the male (sperm) and female (egg) sex cells.

**Stem cell definitions:**
**Embryonic germ (EG) cells**: Pluripotent stem cells derived from cells in the fetal gonad that would normally develop into mature gametes.
**Embryonic stem (ES) cells**: Pluripotent stem cells derived from the inner cell mass of a blastocyst stage embryo.
**Pluripotent stem cell**: A stem cell with the capacity to differentiate into cells of all germ layers (endoderm, ectoderm, and mesoderm). These are usually derived from early embryos or embryonic germ cells.
**Stem cell**: A cell that has the ability to divide for indefinite periods in culture and to give rise to specialized cells.
**Totipotent cells**: Cells of the very early embryo that have the capacity to differentiate into the placenta, the embryo, and all postembryonic tissues and organs. No stem cell line to date has been shown to have these properties.

Appendix ii)

**Members of the *ad hoc* Working Group on Stem Cell Research**

Françoise Baylis: Associate Professor, Dalhousie University, Departments of Bioethics and Philosophy

Timothy Caulfield: Associate Professor, University of Alberta; Research Director, Health Law Institute, University of Alberta

Roger Gosden: Professor, McGill University; Professor & Scientific Director, The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School

Keith Humphries: Professor, University of British Columbia, Department of Medicine; Scientist, BC Cancer Agency, Terry Fox Laboratory

Gregory Korbutt: Assistant Professor, University of Alberta, Department of Surgery; Director, Human Islet Quality Control Laboratory, University of Alberta

Anne McLaren: Principal Research Associate, The Wellcome/CRC Institute of Cancer and Developmental Biology, Cambridge U.K.

Marcel Mélançon : Professeur chercheur en bioéthique, Université du Québec à Chicoutimi

Samuel Weiss: Professor, University of Calgary, Department of Cell Biology and Anatomy

Barbara Beckett: Stem Cell Network, University of Ottawa (rapporteur for the Working Group).

Appendix iii)

## The Public Consultation

On March 29th 2001, CIHR released a Discussion Paper prepared by the *ad hoc* Working Group on Stem Cell Research. The document was publicized in the media, posted on the CIHR web site, and sent to charitable and professional organizations and Canadian institutions that receive CIHR funding. Feedback was invited during a three-month consultation period that ended on June 29th 2001. Some responses were received after this date and these were also taken into consideration.

During the consultation period, on May 3rd 2001, Health Canada released a proposal for draft legislation on assisted human reproduction. The Health Canada proposal addressed issues related to stem cell research and proposed regulations similar to the CIHR guidelines. Both of these announcements generated considerable media interest.

The Working Group received a total of 116 responses. 27 of these were from special interest groups, professional groups, health charities, or government agencies. 89 were from individuals. The Working Group heard a range of opinions from allowing the use of cloning technologies including those leading to the cloning of whole human beings, to allowing research on human embryos under strictly regulated conditions, to prohibiting any research on human embryos. The concerns raised generally reflect those expressed in other consultation processes. Some of these are described in the NIH guidelines of August 2000 (www.nih.gov.news/stemcell/stemcellguidelines.htm), in debates in the House of Commons (www.publications.parliament.uk/pa/cm199900/cmhansrd/vo001117/debtext/01117-01.htm#01117-01_head0; www.publications.parliament.uk/pa/cm200001/cmhansrd/vo001219/debtext/01219-07.htm#01219-07_head0) and the House of Lords (publications.parliament.uk/pa/ld200001/ldhansrd/vo010122/text/10122-04.htm#10122-04_head2) in the U.K. during debates surrounding revision of the HFE Act, and in news media coverage of President Bush's decision. The Working Group respects the diversity of public opinion on this issue and recognizes that there is a need for continuing public debate.

The consultation process was very useful in identifying many areas of concern, all of which were considered in re-drafting the final report to CIHR Governing Council. The research guidelines proposed in this final report help to clarify what research is eligible for CIHR funding and under what conditions.

The following discussion highlights the most commonly expressed concerns.

*Many respondents expressed the viewpoint that the embryo has full moral status and an inviolable right to life from the moment of conception. A number of these respondents also stated that the ethical framework for the proposed recommendations was not discussed or justified.*

While the Working Group respects the diverse viewpoints of respondents on this issue, no attempt was made to articulate an argument regarding the moral status of the embryo, as this was not within the mandate of the Working Group. The principles governing "Human Pluripotent Stem Cell Research: Recommendations for CIHR-funded Research" are the CIHR principles for research involving humans as outlined in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS). The Working Group accepted the TCPS guidelines for research involving human embryos. These guidelines are based on a "graduated approach that correlates permitted interventions with the developmental stages of the human embryo or foetus" **(page 9.1),** and they allow research on embryos until 14 days. This position is consistent with the preponderance of opinion in other international documents.

Some respondents suggested that the reasoning behind restricting embryo research to "spare" embryos was flawed. It should be noted that the distinction between embryos created for *in vitro* fertilization but surplus to the needs of individuals or couples receiving fertility treatment ("spare" embryos), and embryos created for research, was not introduced by the Working Group, but is found in the TCPS. While the moral status of an embryo does not depend on the circumstances of its creation, this distinction may be useful as a measure to preclude or minimize the commodification of human life.

*Many respondents pointed out that adult stem cells may have a previously unanticipated ability to reprogram into other cell types, and that consequently there should be no need to do research on human embryonic stem cells.*

The final document clearly notes the nature and benefits of adult stem cell research, and the guidelines provided apply to the research use of such cells. Adult stem cell research has been and will continue to be a major focus of stem cell research in Canada. However, the international scientific consensus is that research should proceed with all available stem cell types, including embryonic stem cells and embryonic germ cells from fetal tissue, to further explore the potential therapeutic benefits of all research avenues.

*Many respondents expressed concern that an increasing demand for human embryos or fetal material could result in coercion of couples involved in fertility treatment or women considering therapeutic abortion.*

The Working Group is greatly concerned about the possibility that an increase in demand for embryos and fetal tissue could lead to pressure on women to agree to the donation of eggs or fetal material, or to the formation of additional embryos for research use. These potential problems have been addressed in this report in a number of ways. For example,

1) The recommendations require that stem cell lines produced as a result of CIHR-funded research be available to all Canadian researchers on a cost-recovery basis. This should minimize the need for generating large numbers of cell lines which, in turn, should decrease the need for donation of a large numbers of embryos.
2) The recommendations require full disclosure of information by the researchers and free and informed consent from the research participants. Significantly, consent for the research use of embryos must be provided twice – at the time that gametes are provided and again when the research use of the discarded embryos is anticipated.
3) The recommendations require that consent to the use of unwanted embryos or aborted fetal tissue never be a condition of access to treatment.
4) The recommendations include a number of measures aimed at ensuring voluntariness and minimizing the risk of coercion. For example, there are the requirements that the physician responsible for the fertility treatment, the person seeking a consent to the disposition of embryos or the physician responsible for the therapeutic abortion, not be part of the stem cell research team.
5) The recommendations call for the creation of a national oversight body, one of whose important functions would be ongoing monitoring of stem cell research.

*Many respondents suggested that allowing research on stem cells derived from human embryos would launch Canadian researchers on a slippery slope leading to cloning of whole human beings, eugenic selection of the human genome, and devaluation of individuals with disabilities.*

The Discussion Paper published by the Working Group in March 2001 and this final report both state unequivocally that research involving somatic cell nuclear transfer into human oocytes – cloning technology – should not be fundable by CIHR. This would apply to use of this technology to create whole beings, or to create research embryos to develop human stem cell lines. This position is consistent with **Article 9.5** of the TCPS, which explicitly prohibits the cloning of human beings by any means including somatic cell nuclear transfer. As well, the proposal for legislation that has just been reviewed by the House of Commons Standing Committee on Health, includes provisions to outlaw the cloning of whole beings and the creation of research embryos. These provisions were endorsed in the December 2001 report by the Standing Committee.

Further, the Working Group has proposed the creation of a National Stem Cell Oversight Committee with a broad mandate to ensure that human stem cell research funded by CIHR is subject to nationally consistent, rigorous scientific and ethical review. The mandate of the Committee would be sufficiently broad (see Recommendations 8.1, 8.4) to allow it to address the range of ethical concerns about human cloning, eugenics, and respect for persons with disabilities that have been identified by some of the respondents. The proposal for legislation includes a provision for a national oversight committee, also endorsed in the report of the Standing Committee. The creation of this oversight committee would ensure that similar standards apply to publicly and privately funded human stem cell research.

The existence of strict funding guidelines, legislation, and rigorous oversight of human stem cell research should minimize the possibility that allowing stem cell research could open the door to unethical practices that some fear would follow.

This report anticipates that at some later date, researchers may propose research involving autologous stem cell transfer in an effort to develop therapeutic options. This might involve the use of SCNT technology. Permission to proceed with such research, however, would require a change to the guidelines and the principles used to justify this would presumably focus on the treatment of disease. The prohibition on the cloning of whole beings, on the other hand, is unequivocal and no change to this position could be justified by citing the principle of treatment of disease. As noted above, prohibition of cloning whole human beings is consistent with all other major national Canadian documents that address the ethical non-acceptability of this practice.

*Many respondents recognized the need for research guidelines to apply to privately funded research as well as publicly funded research*.

The authority of CIHR is limited to the research that it funds - i.e., CIHR has no authority or means to control research in the private sector except by setting an example and lobbying the government. With this document the Working Group sets a high standard for CIHR-funded research and recommends that the federal government adopt similar standards for research in the private sector so that there can be uniform standards for human stem cell research. It is hoped that the proposed research guidelines will be adopted by CIHR and would be the standard by which private sector research would also be judged in the period prior to the introduction of uniform federal rules for all research whether publicly- or privately-funded.

*Some respondents felt that the term "moratorium" used in the discussion paper was not fully explained.*

The Working Group has avoided the use of this term in the final document. Instead there are two clear categories of research—eligible for CIHR funding and ineligible for CIHR funding. As well, there is a recommendation to CIHR to review stem cell research on an ongoing basis and to revise guidelines as needed (i.e., narrow or broaden the scope of eligible research).

*Some respondents felt that the proposed national ethical oversight committee could make administration of this type of research too complicated and burdensome, and could impose long delays on researchers*.

The Working Group is very sensitive to the problems of bureaucratic delays. However, in an area of research as delicate as human stem cell research, a fully transparent, nationally applicable set of standards is critical. The Working Group hopes that the mandate and mode of action of the proposed National Stem Cell Oversight Committee will not add unnecessary burdens but will assure full accountability.

*Some respondents expressed concern that the Working Group consisted primarily of stem cell researchers or persons closely associated with stem cell research, and that this could represent a potential conflict of interest and could introduce bias into the decisions of the group. Some expressed the view that there should have been representation of the public or other communities on the Working Group.*

Members were chosen on the basis of scientific, ethical, and legal expertise in the area of stem cell research, embryo research and more generally research involving humans. This was appropriate given the mandate of the committee—viz. to recommend research guidelines. It was necessary to include scientists because of their expertise in discussion of complex scientific issues such as the use of adult stem cells vs. embryonic stem cells, the use of chimeras, etc. Some members of the group are not scientists and have no commitment to pursuing stem cell research, but are instead interested in the issues surrounding stem cell research. All members are researchers with a stellar reputation, research and publication record (CVs of the members are available on the CIHR web site [***give address***]). Members of the Working Group agree that having someone from the general public as a member of the Working Group would have been useful, but public opinion was sought and considered through the consultation process.

*A few respondents felt that directing the consultation through the CIHR web site would limit the feedback to certain segments of society and that the specialized nature of the subject and the limitation of the consultation period to three months could introduce bias.*

The original mandate of the Working Group did not include a public consultation phase and it was initially anticipated that the Working Group would report back to the Governing Council of CIHR by June 2001. The consultation was done at the initiative of the Working Group and an extension of the reporting deadline was sought. The Working Group and CIHR also made sure that the document received wide media coverage to ensure that its existence became known to interested parties. The goal was never to do a full survey of Canadians' views on this topic—that would have required a different mandate, budget and time frame. Although the Group's survey of public opinion was limited and possibly biased, it did identify many issues that informed the final report.