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Human Pluripotent Stem Cell Research: Guidelines for CIHR-Funded Research

Foreword
Stem cell research holds great potential to treat human disease and prevent suffering. Stem cells have the potential to provide treatments for a host of debilitating diseases including Alzheimer's, Parkinson's, diabetes, multiple sclerosis, and heart disease. Few other areas of science have generated as much excitement, scrutiny and controversy. At the same time, their derivation and use raise ethical, social issues and legal concerns of interest to Canadians.
At present, Canada has no laws to govern stem cell research, nor are there any guidelines for researchers, research ethics boards, or funding agencies on how stems cells may be derived and used. Recognizing this urgent need for clear guidelines-guidelines that allow for response to rapidly evolving science and shifting public opinion, and ensure ethical and scientific oversight-the Canadian Institutes of Health Research is introducing HUMAN PLURIPOTENT STEM CELL RESEARCH: GUIDELINES FOR CIHR-FUNDED RESEARCH.
Canadian researchers have been pioneers in the area of stem cell research and continue to lead the way using animal models. With the introduction of these guidelines, Canadian researchers will be able to move forward and remain at the forefront of their field while conducting their research according to ethical standards. Funding agencies, Research Ethic Boards, and universities will have a framework to guide their evaluation and approval decisions. Canadians can be assured that the research made possible by federal public funds will be undertaken within a well-defined ethical and legal framework-a framework that does not allow for the use of human embryonic stem cells for the purposes of cloning. I thank the members of the ad hoc Working Group on Stem Cell Research for their significant contribution to the development of these guidelines and Canadians for their thoughtful input, and look forward with great anticipation to the discoveries that lie ahead and the potential health benefits they

HUMAN PLURIPOTENT STEM CELL RESEARCH: GUIDELINES FOR CIHR-FUNDED RESEARCH

The guidelines contained in this document set out the conditions under which the Canadian Institutes of Health Research (CIHR) will fund human pluripotent stem cell research, as well as those types of research that are not eligible for funding.
1.0 Canadian Institutes of Health Research and Ethics in Research CIHR was established by the Government of Canada in 2000 as the federal 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.
CIHR has a duty to ensure that research carried out under its auspices involving humans or human biological material meets the highest ethical standards. 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.
2.0 Development of the Guidelines Given the research potential and the ethical concerns inherent in human pluripotent stem cell research, the CIHR convened 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 Working Group was asked to provide guidance to CIHR as to whether human stem 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.
While research on human adult stem cells was not included in the Working Group's mandate, recent scientific research has raised the possibility of isolating adult stem cells with properties similar to embryonic stem cells. 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 guidelines are worded with that consideration in mind.
An initial Discussion Paper with preliminary recommendations was released in March 2001 as the basis for public

consultation with interested individuals and organizations. This input was incorporated into the development of the Working Group's final report. Their recommendations were adopted by the Governing Council of CIHR in January 2002.
3.0 Guiding principles The guidelines are based on the provisions of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS). Therefore, the guidelines are based on several guiding principles, such as:
Research undertaken should have potential health benefits for Canadians;
Free and informed consent, provided voluntarily and with full disclosure of all information relevant to the consent;
Respect for privacy and confidentiality;
No direct or indirect payment for tissues collected for stem cell research and no financial incentives.
4.0 Oversight of human pluripotent stem cell research
Because of the complex ethical issues and public concern in this area, a Stem Cell Oversight Committee will be created to conduct an ethical review of all human pluripotent stem cell research proposals approved by CIHR's scientific peer review panels. All research proposals will require approval from this Committee, as well as from the local Research Ethics Board (REB), and, where appropriate, the Animal Care Committee (ACC), before being funded. Its members will include experts in stem cell biology and therapeutics, medicine and health care, ethics, law, and social sciences, as well as representatives of the general public. This Committee could also, on request, provide ethical review of human pluripotent stem cell research proposals submitted by other public or private granting agencies. It will also provide advice, on request, to investigators and local REBs on the application of CIHR's Human Pluripotent Stem Cell Research Guidelines.
5.0 Creating a national registry
CIHR will establish an electronically accessible national registry of human embryonic stem cell lines generated in Canada. This registry will minimize the need to generate large numbers of cell lines, which should decrease the need for donation of large numbers of embryos.
All human embryonic stem cell lines generated using CIHR funds will be listed with the registry and made available by the researcher to other Canadian academic researchers, subject to reasonable cost-recovery charges. Participation in this registry will be a prerequisite for obtaining CIHR funding for human pluripotent stem cell research.
6.0 Application of the Guidelines
These guidelines apply to all proposals for human pluripotent stem cell research submitted to CIHR. They do not apply to research proposals to other public sector funding organizations or to the private sector.
However, CIHR will recommend that Health Canada 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 may eventually replace the Stem Cell Oversight Committee.
7.0 Guidelines for CIHR Funding of Human Pluripotent Stem Cell Research in Canada
7.1 Research eligible for CIHR funding The following types of research are eligible for CIHR funding:
7.1.1 Research to derive and study human embryonic stem cell (ES) lines or other cell lines of a pluripotent nature from human embryos, provided that:
The embryos used were originally created for reproductive purposes and are no longer required for such purposes; and There is free and informed consent from all 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 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.
7.1.2 Research to derive and study human embryonic germ cell (EG) lines, or other cell lines of a pluripotent nature from human fetal tissue or amniotic fluid, provided that:
The proposed research does not compromise the pregnant woman's decision on whether to continue her pregnancy, and There is free and informed consent from the pregnant woman.
7.1.3 Research to derive and study human stem cell lines of a pluripotent nature from the umbilical cord and placenta, provided that:
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.
7.1.4 Research to derive and study human stem cell lines of a pluripotent nature from human somatic tissues, provided that:
When the tissue is from a legally competent person, there is free and informed consent from the prospective research participant; or
When the tissue is from a legally incompetent person, the tissue has been obtained from a surgical, diagnostic or other legitimate practice not including research, and an appropriate legally competent third party has authorized its availability for research, and the donation is in accordance with applicable consent law in the province where the donation takes place; or 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 legally competent third party.
7.1.5 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, provided that:
They were created in accordance with CIHR's guidelines. It is incumbent on the recipient of the cell lines to ensure that they were derived in a manner consistent with the CIHR's guidelines. The recipient must provide satisfactory evidence to the local REB and the Stem Cell Oversight Committee that the cell lines fulfill the informed consent provisions before research can begin.
7.1.6 Research involving the grafting of human ES cells, EG cells or other human cells of a pluripotent nature into non-human adults, provided that:
The research is designed to reconstitute a specific tissue or organ to derive a pre-clinical model, and There is evidence from prior studies in non-human species that the cells are not likely to contribute to gametes, and These non-human animals grafted with human stem cells will not be used for reproductive purposes.
7.1.7 Research involving the grafting of human stem cells or other human cells of a pluripotent nature into legally competent humans, provided that:
There is overwhelming evidence from pre-clinical models for safety and efficacy, and The research is carried out in well-designed clinical trials, and There is free and informed consent from the prospective research participants.
7.2 Consent, privacy and confidentiality provisions
7.2.1 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.
7.2.2 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 must be reiterated. 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. A renewal of the consent provided 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.
7.2.3 For the purpose of obtaining free and informed consent to human stem cell research, at a minimum, researchers shall provide prospective research participants or legally competent third parties, in addition to the usual information given:
An explanation that the cell line(s) will be anonymized, except if the research involves autologous donation;
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;
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;
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.
7.2.4 Researchers must not 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.

7.2.5 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.
7.2.6 All researchers who make stem cell lines available to other academics, will ensure that the cell lines are anonymized.
7.2.7 Physicians responsible for fertility treatment and physicians responsible for termination of pregnancy will not be part of a stem cell research team.
7.3 Commercial interest
7.3.1 Researchers or their institutions with financial interests in the outcome of the stem cell research, must disclose this information to the Stem Cell Oversight Committee, the REB and the prospective research participants. In some instances, disclosure may not be a sufficient response to concerns about actual, perceived or potential conflicts of interest.
7.3.2 Copies of contracts between researchers, institutions and industry sponsors and any relevant budgetary information must be provided to the 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. 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 (e.g., cloning).
7.4 Research ineligible for CIHR funding The following types of research are not eligible for CIHR funding:
7.4.1 Research involving the creation of human embryos specifically to derive stem cell lines or other cell lines of a pluripotent nature.
7.4.2 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 (e.g., cloning).
7.4.3 Research involving the directed donation of stem cell lines or, other human cells or cell lines of a pluripotent nature to particular individuals, unless the research involves autologous donation.
7.4.4 Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are combined with a human embryo.
7.4.5 Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are grafted to a human fetus.
7.4.6 Research in which human ES cells, EG cells or other cells of a pluripotent nature are combined with a non-human embryo.
7.4.7 Research in which human ES cells, EG cells or other cells of a pluripotent nature are grafted to a non-human fetus.
8.0 Review CIHR will review the field of human stem cell research on an ongoing basis to redraft the relevant guidelines as needed and, when appropriate, to broaden or narrow the scope of permitted research. This review process will also examine the need for national research ethics review and, when appropriate, amend it.
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