Stem Cell Network
Réseau de cellules souches

Canada's Regulatory Oversight of Stem Cell Research

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Most embryo research takes place in the context of assisted reproductive technology (ART) and as a result, discussion of embryo research ethics and policy falls primarily within that context. In addition, because embryo research involves the use of tissues of men and women, some issues of concern are also discussed in the context of human subjects research policy and regulation.

Enshrined throughout the governing guidelines and policy documents are the principles of free and informed consent, human dignity, the health and welfare of women and children, non-commercialization of gametes and embryos, respect for privacy and confidentiality, and a respect for embryos that requires limits on their use and creation.

Accordingly, Canada's governance of stem cell research is covered by the *Tri-Council Statement: Ethical Conduct for Research Involving Humans* (TCPS). [Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. 1998 (with 2000, 2002 and 2005 amendments)] and the Canadian Institutes of Health Research (CIHR) Guidelines *Updated Guidelines for Human Pluripotent Stem Cell Research* as of June 29, 2007, and the Assisted Human Reproduction Act, chapter 2, Revised Statutes of Canada, 2004. This oversight system had a long and complicated evolution.

The AHRA Regulatory History

In 1989 Prime Minister B. Mulroney appointed the Royal Commission on New Reproductive Technologies (Royal Commission) to examine the social, legal and ethical implications of developments in reproductive technology. Meetings and public consultation were held over a period of two years and the commission issued its final report, *Proceed with Care: the Final Report of the Royal Commission on New Reproductive Technologies* in November 1993. The report recommended several practices be prohibited and that a national assisted reproductive technology (ART) oversight body be created. Drawing on the recommendations of the Commission, the Minister of Health issued a voluntary moratorium on nine reproductive technology practices in July 1995. Relevant to stem cell research were the inclusion of human embryo cloning and the creation of animal-human hybrids.

Bill C-47, a federal law, was drafted in which the recommendations of the Royal Commission were partially incorporated, including the ban of 13 reproductive technology practices. The proposed *Human Reproductive and Genetic Technologies Act* included a ban on creating embryos for research, contrary to the recommendation of the Royal Commission. It also did not seek to establish a national regulatory and licensing body as recommended by the Royal Commission. The Bill died on Order Paper in April 1997.

After a long period of public and policy consultation Parliament enacted the Assisted Human Reproduction Act (AHRA) in March 2004 ending over a decade and a half of attempts to create national ART policy. The AHRA is a national regulatory scheme in which controlled activities may only be done subject to a license. The AHRA is modeled on the United Kingdom's Human Ferilisation and Embryology Act, 1990. While the AHRA covers the derivation of embryonic stem cell lines, it does not cover secondary use of those cell lines.

Sections 5 and 7 of the AHRA outline acts that are prohibited and subject to criminal sanction. These include:

- reproductive and therapeutic/research human cloning (s.5(1)(a))
- creating in vitro embryos for any purpose other than to create a human being (or for improving or providing instruction in AHR procedures) (s.5(1)(b))
- creating one embryo from a cell, or any other part, of another embryo or fetus for reproductive purposes, or transplanting an embryo so created into a human being (s.5(1)(c))
- maintaining an embryo outside the female body for more than 14 days (s.5(1)(d))
- sex selection (except to prevent, diagnose or treat a sex-linked disorder or disease) (s.5(1)(e))
- germ-line gene alteration (s.5(1)(f))
- the transfer of a non-human sperm, ovum, embryo or fetus into a human (s.5(1)(g))
- the use of any human reproductive tissue or in vitro embryos that has previously been implanted in a non-human (s.5(1)(h))
- the creation of a chimera, or the transplant of a chimera into a human or non-human life form (s.5(1)(i)) NB: Chimera means an embryo into which a cell of any non-human life form has been introduced; or b) an embryo that consists of cells of more than one embryo, fetus or human being
- the creation of a hybrid for reproductive purposes (s.5(1)(j))
- the purchase, offer to purchase or advertise for the purchase of human gametes from a donor or a person acting on their behalf (s.7(1))
- the purchase, offer to purchase, or advertisement for the purchase of an in vitro embryo (s.7(2))
- offering a donor to purchase, or to advertise for the purchase of, a human cell (or gene), for the purpose of creating a human being (s.7(3))

Of particular interest are the prohibitions against cloning for research purposes, the creation of embryos for research purposes and the criminalization of commercial transactions in human reproductive tissues.

Tri-Council Policy Statement

In 1994 the three research councils responsible for funding research in the medical, natural and social sciences began work on a joint policy on human experimentation. The Medical Research Council (MRC), National Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC) formed a working group that issued three working papers for public and academic discussion in 1994, 1996 and 1997. The Councils issued the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) in September 1998. The TPCS is mandatory only for those individuals and institutions applying for or receiving funding from any of the three federal government research councils, or those institutions choosing to be bound by the standards. When a controversy over the independence of researchers at the Hospital for Sick Children in Toronto erupted, the MRC indicated that it would try and expand the policy statement to all research involving humans, even that with private funding. To date this expansion has not been effected. The TPCS has no legal force per se on privately-funded researchers. It may, however, have persuasive or moral force in that it articulates accepted standards for ethical practice.

The TCPS contains specific guidance with respect to research involving human embryos. It states that it is not ethically acceptable to create human embryos specifically for research purposes. However, in those cases in which human embryos are created for reproductive purposes and subsequently are no longer required for such purposes, research involving human embryos may be considered ethically acceptable, though certain conditions are imposed. The ova and sperm from which the embryo was formed must have been obtained from individuals who have given free and informed consent and the ova and sperm must not have been obtained through commercial transactions.

The following articles in the TPCS would apply to human embryonic stem cell (hES) research:

- Embryos may not be created for research purposes (Art. 9.4)

This article would seem to limit the ability of Canadian researchers to investigate the mechanisms of hES formation and cell differentiation, as the only source of embryos for research would be surplus embryos from in vitro fertilization (IVF). It does not, however, inhibit the derivation of stem cells from embryos.

- Surplus embryos created for fertility treatments may be used in research if the gamete donors give free and informed consent to the use of the embryos in research. (Art. 9.4)
- Research involving human embryos must take place during the first 14 days after their formation. (Art. 9.4(d))
- It is not ethically acceptable to create, or intend to create, a hybrid individual by such means as mixing human gametes and other animal gametes, or transferring somatic or germ cell nuclei between cells of humans and other species. (Art. 9.3)
- Research ethics board (REB) review is required for research involving human tissue, human embryos or fetuses. (Art. 1.1(b))
- Research is acceptable only if it does not involve the genetic alteration of human gametes or embryos. (Art. 9.4(b))

Additionally, articles 9.1, 9.4 and 10.2 provide information on the informed consent process when using human gametes, embryos and other tissues. The information that must be communicated to prospective tissue donors includes the purposes of the research, any identifiers that might link the donor to the tissue used in research, potential commercial uses of the tissue, and implications for donor privacy.

Policies addressing the use of fetal tissue for therapy indicate consensus that the guiding principles in this regulation should be respect for the woman's dignity and integrity, and respect for human life. The limitations on research involving fetal tissue in the TPCS include the need to obtain free and informed consent to use the tissue, the need not to interfere with the woman's decision to continue or terminate her pregnancy, the prohibition against directed donation, and REB approval.

The TCPS was written prior to the creation of CIHR and AHRA guidelines. Work to amend the TCPS to reflect these recent regulatory changes has been ongoing. In December, 2008 a 2nd draft of the amended TCPS was released for public comment. That version incorporates references to both the AHRA regulations and the CIHR guidelines.

The Canadian Institutes of Health Research Updated Guidelines for Human Pluripotent Stem Cell Research, June 29, 2007[1]

Filling the regulatory gap in 2002, the Canadian Institutes of Health Research (CIHR) announced guidelines for human pluripotent stem cell research. The Guidelines established a national stem cell protocol review board, the Stem Cell Oversight Committee (SCOC), to work in tandem with local REBs and where necessary the appropriate Animal Care Committee. The federal granting agencies, the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC) (the Agencies) subsequently adopted interim Tri-Agency stem cell measures, agreeing that no research with human pluripotent stem cells would be funded without the prior review and approval of the SCOC. The measures incorporate adherence to the Guidelines as a condition of Agency-funded research, and were adopted to afford time to integrate the Guidelines into the *Tri-Council Policy Statement: Ethical Conduct* for Research Involving Humans.

The CIHR Guidelines apply to both the derivation of pluripotent stem cells from human embryos and other tissues and to research using hES lines that have already been derived. They also cover all pluripotent stem cells regardless of their source. So, if adult stem cells can be "reprogrammed" to become pluripotent, the CIHR guidelines would apply. The same is true for induced pluripotent stem cells (iPS), if they are truly pluripotent.

All human embryonic stem cell lines generated using CIHR funds or derived by an institution receiving funds from any of the research councils, will be listed in the national Embryonic Stem Cell Registry. These lines will be made available by the responsible researcher to other academic researchers, subject to reasonable

1 http://www.cihr-irsc.gc.ca/e/34460.html, accessed May 28, 2008

cost-recovery charges. Participation in the registry will be a prerequisite for obtaining CIHR funding for human embryonic stem cell research. 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.

Since the CIHR guidelines are drawn from the TPCS, the principles of free and informed consent by any tissue donors including the donors of gametes and the parents of newborns (if the umbilical cord blood is to be used) run through the guidelines.

Section 8 of the CIHR guidelines sets out the requirements for research that is eligible for CIHR funding. Pursuant to Section 8.1.1, research to derive and study hES lines or other cell lines of a pluripotent nature from human embryos is eligible for CIHR funding, provided that:

- The embryos used were originally created for reproductive purposes and are no longer required for such purposes,
- There is free and informed consent from all the persons for whom the embryos were originally created for reproductive purposes, including consent for research purposes, and
- No commercial transactions including exchange for services were involved in the creation of or donation of the gametes or embryos.

Pursuant to Section 8.1.2, 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 is eligible for CIHR funding, 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.

Pursuant to Section 8.1.6, research involving the grafting of hES, EG cells or other human cells of a pluripotent nature into non-human animals is eligible for CIHR funding, provided that:

- The research is designed to constitute a specific tissue or organ to derive a preclinical model, and
- These non-human animals grafted with human stem cells will not be used for reproductive purposes.[2]

Pursuant to Section 8.1.7, 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:

- There is overwhelming evidence from preclinical models of safety and efficacy,
- The research is carried out in well-designed clinical trials, and
- There is free and informed consent from prospective research participants.

Section 8.3.3 provides that stem cell lines should be anonymized (except if research involves autologous donation), and places the onus upon researchers who make their stem cell lines available to other researchers to ensure the anonymization of their lines. Section 8.3.4 also prohibits conflict of interest scenarios by prohibiting physicians responsible for fertility treatment or pregnancy termination be involved in stem cell research, and researchers from pressuring members of the fertility team to create more embryos than necessary. Section 8.2 sets out the types of research that are not eligible for CIHR funding. These are as follows:

- Creating embryos to use in the derivation of stem cells,
- Research involving somatic cell nuclear transfer into human oocytes for the purposes of developing human embryonic stem cell lines or to the cell lines of a pluripotent nature (e.g., cloning),
- 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,
- Research in which human or non- human ES cells, EG cells or other cells of a pluripotent nature are combined with a human embryo,
- Research in which human or non- human ES cells, EG cells or other cells of a pluripotent nature are grafted to a human fetus,
- Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are combined with a non-human embryo, and
- Research in which human or non-human ES cells, EG cells or other cells of a pluripotent nature are grafted to a non-human embryo.

2 For a discussion of ethical issues associated with the creation of chimeras and use of non-human animals in stem cell research see Knowles L., "Ethics of Stem Cell Research Using Hybrids, Chimeras and Cytoplasmic Hybrids" Stem Cell Network.

The United States

From August 9, 2001 to March 9, 2009 federal law prohibited the use of federal funds for embryo research; therefore the derivation of ES cells could not be performed using federal funds. In August 2001, President G. W. Bush declared that federal funds could be used to perform stem cell research on hES lines existing at that time but not on future cell lines. Although it was originally believed that there were sixty to seventy appropriate cell lines, it now appears that there are fewer than ten hES lines available for NIH funding. On March 9, 2009 by executive order, President B. Obama revoked the funding restrictions put in place by past president G. W. Bush. The executive order entitled "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells" permits the NIH to "support and conduct responsible scientifically worthy human stem cell research, including human embryonic stem cell research to the extent permitted by law."[3] While this will enable hundreds of stem cell lines previously derived to be eligible for federal research dollars, it does not enable federal funding for the derivation of hES. This is due to the annual passage by Congress of the Dickey Wicker amendment which bans the use of federal funds in research that creates human embryos for research or involves the destruction of human embryos.

There is no federal policy that applies to hES research conducted in the private sector, although a number of states have taken it upon themselves to promote or restrict hES research. The first state to enact such a law was California in 2002. The Californian law encourages hES and adult stem cell research, including research-cloning techniques and provides state funding for such work, although it has been mired in legal and practical difficulties. This state has become a model for other states wishing to support hES research.[4]

International Regulation

Around the world countries, scientific associations and international groups have responded to the isolation of hES in a myriad of ways. Some countries have existing regulatory frameworks within which hES research falls. Many others, however, recognizing the potential that hES research holds, have created exceptions in their existing regulatory structures to accommodate, promote or restrict hES research.[4]

Generally a distinction is drawn between using excess embryos from IVF procedures and creating new embryos explicitly for the purposes of research. Additionally, only a few countries permit the use of cloning techniques to create embryos for research purposes, regardless of the potential for autologous transplantation using hES. Finally, most countries have clearly articulated prohibitions against human reproductive cloning. The regions of the world which currently have the most liberal regulatory regimes with respect to hES research, are Israel, the United Kingdom, Belgium, Singapore, China, South Korea and India.

Since the announcements of the isolation of hES in 1998, numerous countries have grappled with whether and to what extent to permit research on embryos. The issue of permissible uses of embryos in research has been largely revisited since stem cell research revealed that these cells hold great therapeutic promise. Countries such as France and Germany with restrictive embryo research policies have loosened their restrictions to permit hES research to take place. Countries like Britain, Sweden and Israel with permissive embryo research regimes have gone farther to permit broad hES research. Some countries continue to have policies that forbid any interventions with the human embryo that are not in its benefit and, therefore, no embryo research is permitted in these countries. Ireland, Austria, and Italy fall into this category.

A large number of countries, including Canada, have struggled with how to create a responsible embryo research policy but permit stem cell research from both adult and embryonic sources. Most countries have adopted some legal interpretation of a view that the embryo is something less than a full person, but that it has a special connection with the human community such that it deserves special respect in the form of limits and restrictions on its use in research. Where the use of embryos in research is condoned limits on the use of those embryos include:

3 President B. Obama, Executive Order 13505, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," http://www.whitehouse.gov/the_press_office/Removing-barriers-to-responsible-scientific-research-involving-human-stem-cells/

4 For a detailed discussion of state sponsored stem cell research see Knowles, L. "State-Sponsored Human Stem Cell Research: Regulatory Approaches and Standard Setting" in *States and Stem Cells: Policy and Economic Implications of State-Sponsored Stem Cell Research*, ed. Levine, A.D., 75-111. (Princeton, N.J.: Policy Research Institute for the Region at Princeton University, 2006).

- Embryos and gametes must be donated with free and informed consent.
- Systems for conflicts of interest management must be in place for the procurement of gametes and embryos.
- The science must be valid and high quality (it must not be frivolous).
- No animal models or animal embryos are adequate for the research (human embryos are necessary, no other embryo will do).
- The numbers of embryos must not be excessive (they will not be wasted).
- Research must take place within the first fourteen days after fertilization (not including any time frozen), after which the embryo must be destroyed. This is to avoid using embryos after the first appearance of the primitive streak, which is the precursor to brain development. The primitive streak appears sometime around day 21 and not before day 17.
- Peer review of research protocols, by research ethics boards (REBs in Canada) or institutional review boards (IRBs in the United States). Embryo research protocols are almost always subject to peer review, to determine a number of the issues around scientific validity, necessity of human embryos, etc. Such review keeps unnecessary destruction of embryos to an absolute minimum – something that is important not just for ethical reasons, but also to maintain public support of embryo research.

Despite significant policy and regulatory differences, there are some issues of consensus and contention for all countries trying to create stem cell policy. Issues of relative consensus include the need for informed consent to stem cell research and conflicts of interest management. Issues of contention include the use of embryos created specifically for research, the creation of embryos using a cloning technology called somatic cell nuclear transfer, compensation for and commercialization of gametes and embryos, and the creation of human and non-human animal chimeras. The international regulations form a patchwork that continues to evolve as the science advances. For a comprehensive look at global stem cell regulations see StemGen, World Stem Cell Map, and Database of Laws and Policies.[5]

The International Society for Stem Cell Research (ISSCR) has addressed some of these issues in its *Guidelines for the Conduct of Human Embryonic Stem Cell Research*.[6] The *Guidelines* cover ethical and governance issues within stem cell research related to "pre-implantation stages of human development" and research on the derivation or use of human pluripotent stem cell lines. They also pertain to experiments in which stem cells are combined or implanted in animal hosts, such as chimeric research. Ethical issues discussed in the *Guidelines* include but are not limited to, informed consent, conflicts of interest in tissue procurement, somatic cell nuclear transfer, the use of human embryos and stem cell lines, chimeric research, commercial transactions in embryos and gametes, and storage and access to stem cell lines.

The ISSCR divides research into three categories; the first is research that should be subject to local review committees such as research ethics boards. The second category of research requires a higher level of review such as provided by national regulatory boards. The final level of research is research that should not be pursued because there is no international consensus on the ethical issues associated with the research. The *Guidelines* make an important contribution to the stem cell ethics discussion with respect to research integrity. The *Guidelines* underline the need for professional integrity and encourage stem cell researchers to work in a transparent and truthful manner so that their work is of top quality and can be reproduced by others. In addition, researchers are encouraged to deposit their stem cell lines in repositories or banks so that other researchers can continue to advance the science.

Using Stem Cells in Clinical Trials in Canada

There is great hope that stem cells can be used in clinical trials in humans, but there are also significant scientific and safety hurdles. In January 2009, the United States Food and Drug Administration (FDA) approved the very first human clinical trial of a therapy using hES.[7] That trial will test in 8-10 paralyzed patients whether hES derived early nerve cells (precursor cells) are safe to use in regeneration of spinal cord cells. The hope is that the

5 StemGen, World Stem Cell Map, and Database of Laws and Policies, http://www.stemgen.org/

6 International Society for Stem Cell Research, Guidelines for the Conduct of Human Embryonic Stem Cell Research, http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf

7 Pollack A., "F.D.A. Approves a Stem Cell Trial" *The New York Times* January 23, 2009.

injected cells will help repair the insulation, known as myelin, around nerve cells, restoring the ability of some nerve cells to carry signals. There is also some hope that the injected cells will help damaged spinal cells repair themselves. Geron, the company sponsoring the trial, was first involved in the derivation of hES cells at the University of Wisconsin and holds the primary U.S. patents on the technology and cells.

Geron attempted to obtain approval for the trial earlier, but in May 2008 the FDA issued a clinical hold on the stem cell trial. The F.D.A. indicated that there were still safety concerns and a need for more information before conducting human trials.[8] This clinical trial is a milestone in hES research, and therefore, great attention will be given to its success. Some stem cell scientists are concerned about the Geron trial being the first hES clinical trial. Although the study is a Phase I trial, aimed mainly at testing the safety of the therapy, if the therapy proves unsafe or even if it doesn't work, the backlash could hurt the field for years to come.

If this trial does prove safe there are other phases of clinical trials that will follow, including higher dosage of cells and different patient groups. Ultimately, there will be years of testing and many hurdles to overcome before the treatment would become routinely available to patients. Another stem cell therapy that is currently being readied for clinical trials in humans is a treatment for macular degeneration, an eye disease, developed in Britain. As of yet there are no human clinical trials using hES in Canada.

Concerns about using stem cells in humans include a fear that mouse models may not accurately predict how the cells will act in humans. In addition, there is concern that the differentiation of the stem cells may not be predictable or controllable in humans. Stem cells have a tendency to create tumours when injected into tissue, and this needs to be clearly under control before they can be used in humans. Stem cell lines can be divided into two grades, research grade stem cell lines and clinical trial stem cell lines. Only the latter will be safe for use in clinical trials in humans. Questions remain about whether clinical grade cell lines can be shown with certainty to be free of contamination.

When therapies become available for use in human clinical trials, there are regulatory hurdles that must be passed before clinical trials commence. Clinical trial review and approval are the responsibility of the Health Products and Food Branch (HPFB) of Health Canada. Trials involving drugs and medical devices are the responsibility of the Therapeutic Product Directorate (TPD) while human trials with biological drugs, including blood and blood products, viral and bacterial vaccines, genetic therapeutic products, tissues, organs and xenografts are the responsibility of the Biologics and Genetic Therapies Directorate (BGTD).

Any product to be used in a clinical trial must be authorized by Health Canada under Division 5 of the Food and Drug Regulations in Canada's Food and Drugs Act. The primary intent of Division 5 of the Food and Drug Regulations is to protect the safety of all human subjects. Stem cells therapies qualify as biologics, drug products derived from biological sources. Biologics are listed in Schedule D of Canada's Food and Drugs Act and includes blood products, cells and tissues, gene therapies, vaccines, radiopharmaceuticals and therapeutic products derived through biotechnology.

Good clinical practices

Under the Food and Drug Regulations, sponsors or investigators wishing to proceed with human clinical trials must submit a Clinical Trial Application. Review periods of the applications are 30 days and there is an inspection function carried out by the BGTD to ensure that the clinical trial applicants are adhering to Good Clinical Practice guidelines. The sponsor of a clinical trial must ensure that the clinical trial is conducted in accordance with the International Conference on Harmonization – Good Clinical Practices. These practices cover manufacturing, record keeping, storage, handling, and labeling and safety standards among others.[9]

It is possible that once a stem cell therapy has been approved, biologically similar stem cell therapies might be eligible for a truncated regulatory review if they qualify as "Subsequent Entry Biologics" (SEB). Health Canada has just released a draft guidance document

8 "FDA places Geron's GRNOPC1 IND on Clinical hold" Genetic Engineering and Biotechnology News May 20, 2008, http://www.genengnews.com/news/bnitem.aspx?name=35532088

9 Health Canada, Drugs and Health Products, Clinical Trials, "Notice: Release of New Guidance for Clinical Trial Sponsors: Clinical Trial Applications" No. 03-111696-573, January 20, 2009, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdctanotice_ctddecavis-eng.php

entitled "Information and Submission Requirements for Subsequent Entry Biologics (SEBs)." This document outlines the regulatory review process that Health Canada will use for a biologic that is similar to another biologic that has already been approved for use and has an established track record of data. The term "follow-on" biologic is used by the U.S. Food and Drug Administration to describe biologics with similar medicinal ingredients, and the regulatory framework for these products is currently under debate.[10]

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10 McMahon, E., Reguly, TA, "Follow-on biologics in Canada: A look at the new draft guidelines." Originally published in *Update* 2008, Issue 3, June 08, 2008, http://www.torys.com/Publications/Documents/Publication%20PDFs/AR2008-42.pdf