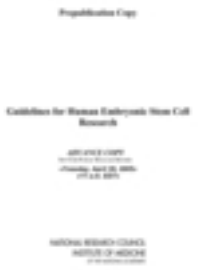

Guidelines for Human Embryonic Stem Cell Research

Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council

ISBN: 0-309-55097-1, 142 pages, 7 x 10, (2005)

6

NATIONAL ACADEMIES GUIDELINES FOR RESEARCH ON HUMAN EMBRYONIC STEM CELLS

1.0 INTRODUCTION

In this chapter we collect all the recommendations made throughout the report and translate them into a series of formal guidelines. These guidelines focus on the derivation, procurement, banking, and use of human embryonic stem (hES) cell lines. They provide an oversight process that will help to ensure that research with hES cells is conducted in a responsible and ethically sensitive manner and in compliance with all regulatory requirements pertaining to biomedical research in general. The National Academies are issuing these guidelines for the use of the scientific community, including researchers in university, industry, or other private-sector research organizations.

1.1(a) What These Guidelines Cover

These guidelines cover all derivation of hES cell lines and all research that uses hES cells derived from

(1) Blastocysts made for reproductive purposes and later obtained for research from in vitro fertilization (IVF) clinics.
(2) Blastocysts made specifically for research using IVF.
(3) Somatic cell nuclear transfer (NT) into oocytes.

The guidelines do not cover research that uses nonhuman stem cells.

Many, but not all, of the guidelines and concerns addressed in this report are common to other areas of human stem cell research, such as

(1) Research that uses human adult stem cells.
(2) Research that uses fetal stem cells or embryonic germ cells derived from fetal tissue; such research is covered by federal statutory restrictions at 42 U.S.C. 289g-2(a) and federal regulations at 45 CFR 46.210.

Institutions and investigators conducting research using such materials should consider which individual provisions of these guidelines are relevant to their research.

1.1(b) Reproductive Uses of NT

These guidelines also do not apply to reproductive uses of nuclear transfer (NT), which are addressed in the 2002 report *Scientific and Medical Aspects of Human Reproductive Cloning*, in which the National Academies recommended that "Human reproductive cloning should not now be practiced. It is dangerous and likely to fail." Although these guidelines do not specifically address human reproductive cloning, it continues to be the view of the National Academies that research aimed at the reproductive cloning of a human being should not be conducted at this time.

1.2 Categories of hES Cell Research

These guidelines specify categories of research that:

(a) Are permissible after currently mandated reviews and proper notification of the relevant research institution.
(b) Are permissible after additional review by an Embryonic Stem Cell Research Oversight (ESCRO) committee, as described in Section 2.0 of the guidelines.
(c) Should not be conducted at this time.
Because of the sensitive nature of some aspects of hES cell research, these guidelines in many instances set a higher standard than is required by laws or regulations with which institutions and individuals already must comply.

1.2(a) hES Cell Research Permissible After Currently Mandated Reviews

Purely in vitro hES cell research that uses previously derived hES cell lines is permissible provided that the ESCRO committee or equivalent body designated by the investigator's institution (see Section 2.0), receives documentation of: i) the provenance of the cell lines; ii) appropriate informed consent in their derivation; and iii) evidence of compliance with any required review by an Institutional Review Board (IRB), Institutional Animal Care and Use Committee (IACUC), or Institutional Biosafety Committee (IBC), or other mandated review.

1.2(b) hES Cell Research Permissible Only After Additional Review and Approval

(1) Generation of new lines of hES cells by whatever means.
(2) Research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development; particular attention should be paid to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.
(3) Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

1.2(c) hES Cell Research That Should Not Be Permitted At This Time

The following types of research should not be conducted at this time:

(1) Research involving in vitro culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.
(2) Research in which hES cells are introduced into nonhuman primate blastocysts or in which any embryonic stem cells are introduced into human blastocysts.

In addition:

(3) No animal into which hES cells have been introduced at any stage of development should be allowed to breed.

1.3 Obligations of Investigators and Institutions

All scientific investigators and their institutions, regardless of their field, bear the ultimate responsibility for ensuring that they conduct themselves in accordance with professional standards and with integrity. In particular, people whose research involves hES cells should work closely with oversight bodies, demonstrate respect for the autonomy and privacy of those who donate gametes, blastocysts, or somatic cells and be sensitive to public concerns about research that involves human embryos.

2.0 ESTABLISHMENT OF AN INSTITUTIONAL EMBRYONIC STEM CELL RESEARCH OVERSIGHT COMMITTEE

To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution involved in hES cell research should establish an Embryonic Stem Cell Research Oversight (ESCRO) committee. The committee should include representatives of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research. It must have suitable scientific, medical, and ethical expertise to conduct its own review and should have the resources needed to coordinate the management of the various other reviews required for a particular protocol. A pre-existing committee could serve the functions of the ESCRO committee provided that it has the recommended expertise and representation to perform the various roles described in this report. For example, an institution might elect to constitute an ESCRO committee from among some members of an IRB. But the ESCRO committee should not be a subcommittee of the IRB, as its responsibilities extend beyond human subject protections. Furthermore, much hES cell research does not require IRB review. The ESCRO committee should:

1) Provide oversight over all issues related to derivation and use of hES cell lines.
2) Review and approve the scientific merit of research protocols.
3) Review compliance of all in-house hES cell research with all relevant regulations and these guidelines.

4) Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators.
5) Facilitate education of investigators involved in hES cell research.

3.0 PROCUREMENT OF GAMETES, BLASTOCYSTS OR CELLS FOR hES GENERATION

3.1. An IRB, as described in federal regulations at 45 CFR 46.107, should review the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines, including the procurement of blastocysts in excess of clinical need from infertility clinics, blastocysts made through IVF specifically for research purposes, and oocytes, sperm, and somatic cells donated for development of hES cell lines derived through NT or by parthenogenesis or androgenesis.

3.2. Consent for donation should be obtained from each donor at the time of donation. Even people who have given prior indication of their intent to donate to research any blastocysts that remain after clinical care should nonetheless give informed consent at the time of donation. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

3.3. When donor gametes have been used in the IVF process, resulting blastocysts may not be used for research without consent of all gamete donors.

3.4a. No payments, cash or in-kind, may be provided for donating blastocysts in excess of clinical need for research purposes. People who elect to donate stored blastocysts for research should not be reimbursed for the costs of storage prior to the decision to donate.

3.4b. Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. No payments, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments should be made for donations of sperm for research purposes or of somatic cells for use in NT.

3.5. To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research. Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.

3.6. In the context of donation of gametes or blastocysts for hES cell research, the informed consent process, should, at a minimum, provide the following information.

a. A statement that the blastocysts or gametes will be used to derive hES cells for research that may include research on human transplantation.

b. A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.
c. A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES cell lines.
d. If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.
e. An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, must be secured to ensure confidentiality.)
f. A statement that derived hES cells and/or cell lines might be kept for many years.
g. A statement that the hES cells and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models.
h. Disclosure of the possibility that the results of study of the hES cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development;
i. A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.
j. A statement that embryos will be destroyed in the process of deriving hES cells.
k. A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.
l. A statement of the risks involved to the donor.

In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but might not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored.

3.7. Clinical personnel who have a conscientious objection to hES cell research should not be required to participate in providing donor information or securing donor consent for research use of gametes or blastocysts. That privilege should not extend to the care of a donor or recipient.

3.8. Researchers may not ask members of the infertility treatment team to generate more oocytes than necessary for the optimal chance of reproductive success. An infertility clinic or other third party responsible for obtaining consent or collecting materials should not be able to pay for or be paid for the material obtained (except for specifically defined cost-based reimbursements and payments for professional services).

4.0 DERIVATION OF hES CELL LINES

4.1. Requests to the ESCRO committee for permission to attempt derivation of new hES cell lines from donated embryos or blastocysts must include evidence of IRB approval of the procurement process (see Section 3.0 above).

4.2. The scientific rationale for the need to generate new hES cell lines, by whatever means, must be clearly presented, and the basis for the numbers of embryos and blastocysts needed should be justified.

4.3. Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES cells before permission to derive new lines is given.

4.4. When NT experiments involving either human or nonhuman oocytes are proposed as a route to generation of ES cells, the protocol must have a strong scientific rationale. Proposals that include studies to find alternatives to donated oocytes in this research should be encouraged.

4.5. Neither blastocysts made using NT (whether produced with human or nonhuman oocytes) nor parthenogenetic or androgenetic human embryos may be transferred to a human or nonhuman uterus or cultured as intact embryos *in vitro* for longer than 14 days or until formation of the primitive streak, whichever occurs first.

4.6. Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines and how they will maintain the confidentiality of any coded or identifiable information associated with the lines (see Section 5.0 below).

5.0 BANKING AND DISTRIBUTION OF hES CELL LINES

There are several models for the banking of human biological materials, including hES cells. The most relevant is the U.K. Stem Cell Bank. The guidelines developed by this and other groups generally adhere to key ethical principles that focus on the need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells—that is, that they were obtained ethically and with the informed consent of donors, that they are well characterized and screened for safety, and that the conditions under which they are maintained and stored meet the highest scientific standards. Institutions engaged in hES research should seek mechanisms for establishing central repositories for hES cell lines—through partnerships or augmentation of existing quality research cell line repositories and should adhere to high ethical, legal, and scientific standards. At a minimum, an institutional registry of stem cell lines should be maintained.

5.1 Institutions that are banking or plan to bank hES cell lines should establish uniform guidelines to ensure that donors of material give informed consent through a process approved by an IRB and that meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and common guidelines for distribution of cells should be established.

5.2 Any facility engaged in obtaining and storing hES cell lines should consider the following standards:

a. Creation of a committee for policy and oversight purposes and creation of clear and standardized protocols for banking and withdrawals.

b. Documentation requirements for investigators and sites that deposit cell lines, including

i. A copy of the donor consent form.
ii. Proof of Institutional Review Board approval of the procurement process.
iii. Available medical information on the donors, including results of infectious-disease screening.
iv. Available clinical, observational, or diagnostic information about the donor(s).
v. Critical information about culture conditions (such as media, cell passage, and safety information).
vi. Available cell line characterization (such as karyotype and genetic markers).

A repository has the right of refusal if prior culture conditions or other items do not meet its standards.

c. A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to

i. A schema for maintaining confidentiality (such as a coding system).
ii. A system for a secure audit trail from primary cell lines to those submitted to the repository.
iii. A policy governing whether and how to deliver clinically significant information back to donors.

d. The following standard practices:

i. Assignment of a unique identifier to each sample.
ii. A process for characterizing cell lines.
iii. A process for expanding, maintaining, and storing cell lines.
iv. A system for quality assurance and control.
v. A Website that contains scientific descriptions and data related to the cell lines available.
vi. A procedure for reviewing applications for cell lines.
vii. A process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).
viii. A system for auditing compliance.
ix. A schedule of charges.
x. A statement of intellectual property policies.
xi. When appropriate, creation of a clear Material Transfer Agreement or user agreement.

xii. A liability statement.
xiii. A system for disposal of material.

e. Clear criteria for distribution of cell lines, including but not limited to evidence of approval of the research by an embryonic stem cell research oversight committee or equivalent body at the recipient institution.

6.0 RESEARCH USE OF hES CELL LINES

Once hES cell lines have been derived, investigators and institutions, through ESCRO committees and other relevant committees (such as an IACUC, an IBC, or a radiation safety committee) should monitor their use in research.

6.1 Institutions should require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally. Notice to the institution should include evidence of IRB-approval of the procurement process, evidence of and adherence to basic ethical and legal principles of procurement. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

6.2. *In vitro* experiments involving the use of already derived and coded hES cell lines will not need review beyond the notification required in Section 6.1.

6.3. Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding the use of hES cells.

6.4. All protocols involving the combination of hES cells with nonhuman embryos, fetuses, or adult animals must be submitted to the local IACUC for review of animal welfare issues and to the ESCRO committee for consideration of the consequences of the human contributions to the resulting chimeras. (See also Section 1.2(c)(3) concerning breeding of chimeras.)

6.5. Transplantation of differentiated derivatives of hES cells or even hES cells themselves into adult animals will not require extensive ESCRO committee review. If there is a possibility that the human cells could contribute in a major organized way to the brain of the recipient animal, however, the scientific justification for the experiments must be strong, and proof of principle using nonhuman (preferably primate) cells, is desirable.

6.6. Experiments in which hES cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses and allowed to develop into adult chimeras need more careful consideration because the extent of human contribution to the resulting animal may be higher. Consideration of any major functional contributions to the brain should be a main focus of review. (See also Section 1.2(c)(3) concerning breeding of chimeras.)

6.7. Introduction of hES cells into nonhuman mammalian blastocysts should be considered only under circumstances in which no other experiment can provide the information needed. (See also

Sections 1.2(c)(2) and 1.2(c)(3) concerning restrictions on breeding of chimeras and production of chimeras with nonhuman primate blastocysts.)

6.8 Research use of existing hES cells does not require IRB review unless the research involves introduction of the hES cells or their derivatives into patients or the possibility that the identity of the donors of the blastocysts, gametes, or somatic cells is readily ascertainable or might become known to the investigator.

7.0 INTERNATIONAL COLLABORATION

7.1 If a U.S.-based investigator collaborates with an investigator in another country, the ESCRO committee may determine that the procedures prescribed by the foreign institution afford protections consistent with these guidelines, and the ESCRO committee may approve the substitution of some of or all of the foreign procedures for its own.

8.0 CONCLUSION

The substantial public support for hES cell research and the growing trend by many nonfederal funding agencies and state legislatures to support this field requires a set of guidelines to provide a framework for hES cell research. In the absence of the oversight that would come with unrestricted federal funding of this research, these guidelines will offer reassurance to the public and to Congress that the scientific community is attentive to ethical concerns and is capable of self-regulation while moving forward with this important research.

To help ensure that these guidelines are taken seriously, stakeholders in hES cell research—sponsors, funding sources, research institutions, relevant oversight committees, professional societies, and scientific journals, as well as investigators—should develop policies and practices that are consistent with the principles inherent in these guidelines. Funding agencies, professional societies, journals, and institutional review panels can provide valuable community pressure and impose appropriate sanctions to ensure compliance. For example, ESCROs and IRBs should require evidence of compliance when protocols are reviewed for renewal, funding agencies should assess compliance when reviewing applications for support, and journals should require that evidence of compliance accompanies publication of results.

As individual states and private entities move into hES cell research, it will be important to initiate a national effort to provide a formal context in which the complex moral and oversight questions associated with this work can be addressed on a continuing basis. Both the state of hES cell research and clinical practice and public policy surrounding these topics are in a state of flux and are likely to be so for several years. Therefore, the committee believes that a national body should be established to assess periodically the adequacy of the policies and guidelines proposed in this document and to provide a forum for a continuing discussion of issues involved in hES cell research. New policies and standards may be appropriate for issues that cannot now be foreseen. The organization that sponsors this body should be politically independent and without conflicts of interest, should be respected in the lay and scientific communities, and able to call on suitable expertise to support this effort.