

# UMBI Embryonic Stem Cell Research Oversight (ESCRO) Committee

## Scope of ESCRO Review of Human Embryonic Stem (hES) Cell and Pluripotent Stem Cell Research

### I. Research requiring full ESCRO Review:

#### A. Derivation:

1. Protocols for the derivation of new lines from pre-implantation embryos.
2. All research performed with the intention of experimentally creating a human embryo by any means, including, but not limited to parthenogenesis, androgenesis, or nuclear/chromosome transfer.
3. Any research that inadvertently produces a human embryo needs to be reported to the ESCRO immediately.

#### B. Use:

1. All research in which the identity of the donors of embryos, blastocysts, gametes, somatic cells or other tissues from which hES cells were derived is readily ascertainable or might become known to the investigator.
2. All research involving the introduction of human pluripotent cells (from any source, including but not limited to hES cells, those derived from human somatic cells, amniotic fluid, or fetal tissue) into any non-human animal at any stage of prenatal development (NB, insertion of human pluripotent cells into primate blastocysts is prohibited).<sup>1</sup>
3. All research involving the insertion of human pluripotent cells or human nerve stem cells into the central nervous system of any non-human animal.
4. All research involving the introduction of human pluripotent cells into humans.

### II. Research eligible for expedited ESCRO review:

#### A. Use:

1. *In vitro* use of any hESC line not requiring review as listed above.
2. Any chimera research with hESC lines not requiring review as listed above<sup>1</sup>.

<sup>1</sup> Teratoma formation to test for pluripotency does not require ESCRO review.

## **ESCRO Examination of the Provenance of Embryonic Stem Cell Lines**

### **I. Lines requiring examination by the full ESCRO:**

- A. Any non-NIH line derived outside of the University of Maryland Biotechnology Institute (UMBI) (Lines derived at UMBI are considered “outside” the university.)

### **II. Lines eligible for administrative ESCRO examination:**

- A. Any line derived within the University of Maryland Biotechnology Institute (not including affiliates).

- B. Any line included on the NIH registry

Summary of Type of ESCRO Review/Examination

**Embryonic Stem Cell Research Oversight (ESCRO) committees or their equivalents should divide research proposals into three categories in setting limits on research and determining the requisite level of oversight:**

- (a) Research that is permissible after notification of the research institution’s ESCRO committee and completion of the reviews mandated by current requirements. Purely in vitro hES cell research with pre-existing coded or anonymous hES cell lines in general is permissible provided that notice of the research, documentation of the provenance of the cell lines, and evidence of compliance with any required Institutional Review Board, Institutional Animal Care and Use Committee, Institutional Biosafety Committee, or other mandated reviews, is provided to the ESCRO committee or other body designated by the investigator’s institution.
- (b) Research that is permissible only after additional review and approval by an ESCRO committee or other equivalent body designated by the investigator’s institution.

The ESCRO committee should evaluate all requests for permission to attempt derivation of new hES cell lines from donated blastocysts, from in vitro fertilized oocytes, or by nuclear transfer. The scientific rationale for the need to generate new hES cell lines, by whatever means, should be clearly presented, and the basis for the numbers of blastocysts or oocytes needed should be justified. Such requests should be accompanied by evidence of Institutional Review Board approval of the procurement process.

All research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by the ESCRO committee. Particular attention should be paid to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.

Research in which personally identifiable information about the donors of the blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable by the investigator also requires ESCRO committee review and approval.

- (c) Research that should not be permitted at this time.

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.

Research in which hES cells are introduced into nonhuman primate blastocysts or in which any embryonic stem cells are introduced into human blastocysts.

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

#### Informed Consent of Donors

The donors of sperm, oocytes, or somatic cells used to make blastocysts for research are themselves rarely the subject of the research. Nevertheless, the physical interaction needed to obtain the materials brings them under the purview of the human subjects protections system, and IRB review is required. Thus, their fully informed and voluntary consent is required before such research use.

Institutional Review Boards may not waive the requirement for obtaining informed consent from any person whose somatic cells, gametes, or blastocysts are used in hES cell research.

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## Appendix A

### Compilation of Recommendations from National Academies

#### RECOMMENDATIONS FROM CHAPTER 3

##### Recommendation 1:

To provide local oversight of all issues related to derivation and research use of hES cell lines and to facilitate education of investigators involved in hES cell research, all institutions conducting 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. The ESCRO committee would not substitute for an Institutional Review Board but rather would provide an additional level of review and scrutiny warranted by the complex issues raised by hES cell research. The committee would also serve to review basic hES cell research using preexisting anonymous cell lines that does not require consideration by an Institutional Review Board.

##### Recommendation 2:

Through its Embryonic Stem Cell Research Oversight (ESCRO) committee, each research institution should ensure that the provenance of hES cells is documented. Documentation should include evidence that the procurement process was approved by an Institutional Review Board to ensure adherence to the basic ethical and legal principles of informed consent and protection of confidentiality.

##### Recommendation 3:

Embryonic Stem Cell Research Oversight (ESCRO) committees or their equivalents should divide research proposals into three categories in setting limits on research and determining the requisite level of oversight:

- (a) Research that is permissible after notification of the research institution's ESCRO committee and completion of the reviews mandated by current requirements. Purely in vitro hES cell research with pre-existing coded or anonymous hES cell lines in general is permissible provided that notice of the research, documentation of the provenance of the cell lines, and evidence of compliance with any required Institutional Review Board, Institutional Animal Care and Use Committee, Institutional Biosafety Committee, or other mandated reviews is provided to the ESCRO committee or other body designated by the investigator's institution.
- (b) Research that is permissible only after additional review and approval by an ESCRO committee or other equivalent body designated by the investigator's institution.

The ESCRO committee should evaluate all requests for permission to attempt derivation of new hES cell lines from donated blastocysts, from in vitro fertilized oocytes, or by nuclear transfer. The scientific rationale for the need to generate new hES cell lines, by whatever means, should be clearly presented, and the basis for the numbers of blastocysts or oocytes needed should be justified. Such requests should be accompanied by evidence of Institutional Review Board approval of the procurement process.

All research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by the ESCRO committee. Particular attention should be paid to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.

Research in which personally identifiable information about the donors of the blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable by the investigator also requires ESCRO committee review and approval.

(c) Research that should not be permitted at this time:

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.

Research in which hES cells are introduced into nonhuman primate blastocysts or in which any ES cells are introduced into human blastocysts.

In addition:

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

Recommendation 4:

Through its Embryonic Stem Cell Research Oversight (ESCRO) committee, each research institution should establish and maintain a registry of investigators conducting hES cell research and record descriptive information about the types of research being performed and the hES cells in use.

Recommendation 5:

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

Recommendation 6:

A national body should be established to assess periodically the adequacy of the guidelines proposed in this document and to provide a forum for a continuing discussion of issues involved in hES cell research.

Recommendation 7:

The hES cell research community should ensure that there is sufficient genetic diversity among cell lines to allow for potential translation into health-care services for all groups in our society.

RECOMMENDATIONS FROM CHAPTER 4

Recommendation 8:

Regardless of the source of funding and the applicability of federal regulations, an Institutional Review Board or its equivalent should review the procurement of 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 in vitro fertilization clinics, blastocysts made through in vitro fertilization specifically for research purposes, and oocytes, sperm, and somatic cells donated for development of hES cell lines derived through nuclear transfer.

Recommendation 9:

Institutional Review Boards may not waive the requirement for obtaining informed consent from any person whose somatic cells, gametes, or blastocysts are used in hES research.

Recommendation 10:

Investigators, institutions, Institutional Review Boards, and privacy boards should ensure that authorizations are received from donors, as appropriate and required by federal human subjects protections and the Health Insurance Portability and Accountability Act for the confidential transmission of personal health information to repositories or to investigators who are using hES cell lines derived from donated materials.

Recommendation 11:

Investigators and institutions involved in hES cell research should conduct the research in accordance with all applicable laws and guidelines pertaining to recombinant DNA research and animal care. Institutions should consider adopting Good Laboratory Practice standards for some or all of their basic hES cell research.

Recommendation 12:

hES cell research leading to potential clinical application must be in compliance with all applicable Food and Drug Administration (FDA) regulations. If FDA requires that a link to the donor source be maintained, investigators and institutions must ensure that the confidentiality of the donor is protected, that the donor understands that a link will be maintained, and that, where applicable, federal human subjects protections and Health Insurance Portability and Accountability Act or other privacy protections are followed.

RECOMMENDATIONS FROM CHAPTER 5

Recommendation 13:

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

Recommendation 14:

To facilitate autonomous choice, decisions related to the production 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.

Recommendation 15:

No cash or in kind payments may be provided for donating blastocysts in excess of clinical need for research purposes.

Recommendation 16:

Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for nuclear transfer) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an Institutional Review Board. No cash or in kind payments 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 nuclear transfer.

Recommendation 17:

Consent for blastocyst 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.

Recommendation 18:

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

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.

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.

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.

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.)

A statement that derived hES cells and/or cell lines might be kept for many years.

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.

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;

A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.

A statement that embryos will be destroyed in the process of deriving hES cells.

A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.

A statement of the risks involved to the donor.

Recommendation 19:

Consenting or refusing to donate gametes or embryos for research should not affect or alter in any way the quality of care provided to prospective donors. That is, clinical staff must provide appropriate care to patients without prejudice regarding their decisions about disposition of their embryos.

Recommendation 20:

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.

Recommendation 21:

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).

Recommendation 22:

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 Institutional Review Board, 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.

Recommendation 23:

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

A copy of the donor consent form.

Proof of Institutional Review Board approval of the procurement process.

Available medical information on the donors, including results of infectious-disease screening.

Available clinical, observational, or diagnostic information about the donor(s).

Critical information about culture conditions (such as media, cell passage, and safety information).

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

A schema for maintaining confidentiality (such as a coding system).

A system for a secure audit trail from primary cell lines to those submitted to the repository.

A policy governing whether and how to deliver clinically significant information back to donors.

(d) The following standard practices:

Assignment of a unique identifier to each sample.

A process for characterizing cell lines.

A process for expanding, maintaining, and storing cell lines.

A system for quality assurance and control.

A website that contains scientific descriptions and data related to the cell lines available.

A procedure for reviewing applications for cell lines.

A process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).

A system for auditing compliance.

A schedule of charges.

A statement of intellectual property policies.

When appropriate, creation of a clear Material Transfer Agreement or user agreement.

A liability statement.

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.

Review/Examination Type Submission Type	Full-Committee	Expedited <sup>2</sup>	Administrative <sup>3</sup>
Derivation of lines from pre-implantation human embryos	X		
All research performed with the intention of experimentally creating a human embryo by any means	X		
Any research that inadvertently produces a human embryo (submit protocol immediately upon discovery)	X		
Derivation of lines from non-embryonic human sources	ESCRO review not required; other committee reviews may be required		
hESC lines derived within UMBI (not including affiliates)			X
non-NIH registry hESC lines derived outside of UMBI	X		
hESC lines included on the NIH registry			X
hESC lines already accepted by the UMBI ESCRO, regardless of where they were derived	Subsequent examination not required if line has already been accepted by the UMBI ESCRO		
Lines derived from non-embryonic human sources	ESCRO examination not required		
All research in which the identity of donors might become known	X		
All research involving the introduction of human pluripotent cells into any non-human animal at any stage of prenatal development	X		
All research involving insertion of human pluripotent stem cells or human nerve cells into the central nervous system of any non-human animal	X		
All research involving the introduction of human pluripotent cells into humans	X		
<i>In vitro</i> use of any hESC line not listed above		X	
Any chimera research with hESC lines not listed above		X	

<sup>2</sup> Expedited protocol review is performed by the ESCRO Chair or Chair's designee.

<sup>3</sup> Administrative examination of provenance is performed by the ESCRO Administrator.

<sup>4</sup> Embryonic-origin lines must also be registered upon successful derivation.

<sup>5</sup> Use of lines is automatically registered by the ESCRO Office upon protocol approval.