Oakland University
Human Pluripotent Stem Cell Research Oversight (HPSCRO) Committee Guidelines

Background and Purpose

Human pluripotent stem cells (HPSCs) are characterized by having the ability to divide indefinitely and give rise to specialized cell types. HPSCs include both human embryonic stem cells (HESCs) and human induced pluripotent stem cells (HiPSCs). HESCs are derived from the inner cell mass of a blastocyst and can give rise to any tissue of the body. HiPSCs are similar to HESCs and are formed by the introduction of certain embryonic genes or transcription factors into a somatic cell.

Because of their unique properties, HPSCs offer great promise in the understanding and treatment of many human diseases and conditions. However, the derivation and research use of these cells pose many ethical and legal challenges. As such, in addition to state and federal regulations governing their use, other guidelines have been developed to provide recommendations related to the derivation and use of HPSCs in research. Such recommendations include creating a human pluripotent stem cell research oversight (HPSCRO) committee at the institution where the research is conducted to provide local oversight.

The purpose of the Oakland University (OU) HPSCRO Committee is to provide oversight of the derivation of and research use of HESCs and HiPSCs by OU researchers. The OU HPSCRO Committee will provide oversight for both federally funded and non-federally funded research.

The OU HPSCRO Committee Guidelines are based on recommendations of the National Academies' Guidelines (2010) for Human Embryonic Stem Cell Research, the principles of the NIH Guidelines for Research Using Human Stem Cells (2009), Michigan State regulations, and the Office of Human Research Protection regulations pertaining to research involving human subjects.

Definitions (NIH)

Stem cells (SCs): Cells with the ability to divide for indefinite periods in culture and to give rise to specialized cells.

Human embryonic stem cell (HESC): A type of pluripotent stem cell derived from early stage human embryos, up to and including the blastocyst stage. HESCs are capable of dividing for a prolonged period in culture and are known to develop into cells and tissues of the three primary germ layers.

Induced pluripotent stem cell (iPSC): A type of pluripotent stem cell, similar to an embryonic stem cell, formed by the introduction or over expression of certain embryonic genes into a somatic cell.

Pluripotent: The state of a single cell that is capable of differentiating into all tissues of an organism, but alone is not capable of sustaining full organismal development.

Somatic cell nuclear transfer (SCNT): A technique that combines an enucleated egg and the nucleus of a somatic cell to make an embryo. SCNT can be used for therapeutic or reproductive purposes.

Parthenogenesis: The artificial activation of an egg in the absence of sperm; the egg begins to divide as if it has been fertilized.

Charge of the Committee

The OU HPSCRO Committee is charged with providing oversight of all ethical and scientific aspects of research involving the derivation and research use of HPSCs. This oversight is in addition to other compliance committee oversight at OU including the Institutional Review Board (IRB), the Institutional Biosafety Committee (IBC) and the Institutional Animal Care and Use Committee (IACUC). Using recommendations in the Final Report of The National Academies' Human Embryonic Stem Cell Research Advisory Committee (2010), the charge of the committee is to:

- Develop guidelines for researchers related to the derivation and use of HPSCs
- Establish and maintain a registry of HPSCs, including the type of research being conducted, the cell or cell line in use and the provenance of cells
- Maintain records of HPSCRO Committee reviews, approvals and other actions
- Establish categories of review as well as limits on research at each level of review
- Review research protocols requiring review
- Ensure compliance with all relevant regulations and guidelines and other OU compliance oversight committees
- Provide oversight over other issues related to the use of HPSCs not otherwise covered by NIH guidelines

Committee Composition

The HPSRCO committee will be comprised of at least 3 OU faculty with expertise in relevant scientific disciplines such as developmental biology, stem cell research, and molecular biology. Depending on the nature of the research under its review, the committee may include ad hoc consultants in other scientific disciplines, ethics, law, and the lay public as needed.

Members are appointed by the University President at the recommendation of the Associate Vice President for Research (AVPR). Appointments are for a 1-year term and are renewable for an unlimited number of terms.

The committee may also include the Directory of Regulatory Support and the Laboratory Safety Compliance Manager as permanent non-voting Ex-Officio members.

Operation of the HPSCRO Committee

The OU HPSCRO Committee may meet on an ad hoc basis to review proposed research involving HPSCs. The committee may also assist in the development of policies and guidelines related to the derivation and use of HPSCs in research.

The committee may vote to approve, disapprove or require modifications to research proposals under its review. Review decisions will be communicated to researchers within 7 calendar days of the committee's review decision.

A quorum (greater than 50% of members) must be present to review research proposals requiring full committee review or conduct other business. Consultants may not count toward the quorum requirement. Members or consultants may participate in committee meetings via telephone or videoconferencing.

Committee members must comply with the OU Conflict of Interest Policy (AP&P #406) and sign the *Oakland University Human Stem Cell Oversight Committee Conflict of Interest Statement and Confidentiality Agreement*. Any member with a conflict of interest must recuse himself/herself from the review of research in which he/she (or their immediate family member) has a conflict of interest.

Conflicts of interest may include but are not limited to:

- Being listed as an investigator on the research application
- Having a significant financial interest in the sponsor of the research or the technology being developed
- Any other conflict that may be perceived as biasing the review of the research

Conflicts of interest will be reviewed prior to each meeting in which a research proposal is reviewed. The recusal of any member during a meeting will be documented in the meeting minutes.

HPSCRO Committee Staff

The HPSCRO Committee will be administratively supported by regulatory compliance staff in the Research Office. The regulatory compliance staff will be responsible for the following:

- Maintaining a registry of HPSCs used in research, including their uses and provenance
- Processing applications for review including distribution at committee meetings when the proposals require full committee review
- Communicating HPSCRO Committee decisions to researchers within 7 calendar days of the committee's review decision
- Recording and maintaining a record of meeting minutes, committee actions and other documents

HESCs

A. Derivation

Derivation of HESCs will be permitted under the following conditions:

- HESCs must be derived from embryos younger than 14 days old
- Human embryos used to derive HECSs must have been created for fertility treatment and be in excess of or deemed unsuitable for clinical need
- Written informed consent and IRB approval must have been obtained from the donor at the time of human embryo donation for fertility treatment
- Human embryos may not be purchased and there may be no incentives to create embryos for the sole purpose of research
- Donor privacy and confidentiality must be protected

No federally funded salaries, equipment, space, or supplies can be used to derive a new pluripotent stem cell line from a human embryo.

B. Research Use

Impermissible uses of human embryos and HESCs include the following:

- *In vitro* culture of any intact human embryo 14 days or older
- Introduction of HESCs into human and non-human primate blastocysts
- Breeding of any animal into which HESCs have been introduced at any stage of development where the stem cells may contribute to the central nervous system or germline

HiPSCs

A. Derivation

Derivation of HiPSCs will be permitted under the following conditions:

- From donated tissue or somatic cells where IRB approval has been obtained and informed consent has been obtained or waived
- Donor's privacy and confidentiality is protected

B. Research Use

Impermissible uses of HiPSCs include the following:

- Research in which HiPSCs are introduced into human or non-human primate blastocysts
- Research involving breeding of any animal into which HiPSCs have been introduced where the stem cells may contribute to the central nervous system or germline

HPSCRO Application Procedures

Researchers proposing to derive and/or use HPSCs for research purposes must submit an application and supporting documentation to the HPSCRO Committee for review. Applications are designed to capture information regarding the cell line to be derived or obtained, the cell source, provider of the cell line, adequacy of informed consent, scientific rationale/justification and objectives of the proposed research, federal funding restrictions and other compliance requirements. Applications can be found on the OU regulatory compliance web page.

HESCs

Derivation

For derivation of HESCs at OU, informed consent and IRB approval are required for donation of the embryo. Researchers must submit an HPSCRO Committee application describing the derivation and proposed future research uses of the generated cell line. IRB and IBC approval must be obtained prior to derivation of the HESC line and any work on the project. The HPSCRO Committee may, at its discretion, review the consent process with the IRB. Derivation of HESCs will require review and approval by the fully convened HPSCRO Committee. Once approved, the newly generated HESC line will be placed on the HPSCRO Committee internal registry. The HPSCRO Committee will work with researchers to apply for acceptance of the newly derived cell line on the NIH Registry.

Obtaining HESC Lines Derived Outside of OU

HESC lines on the NIH registry and HESC lines not on the NIH registry may be used in research following HPSCRO Committee approval. A Material Transfer Agreement (MTA) is required for all HESC lines obtained from other institutions. A MTA indicates the provenance of the cell line and may be initiated by either OU or the outside institution. Non-NIH registered HESC lines will require submission of documentation that IRB approval and informed consent were properly obtained. When the provenance of the cell line has been determined to be acceptable, the cell line will be added to the OU HPSCRO Committee internal registry. IBC approval is required prior to receipt of HESC lines from outside institutions.

Researchers must submit an application to the HPSCRO Committee describing the provenance and proposed research uses of the requested cell lines. The application will be reviewed and approved by the HPSCRO Committee Chair or a designated member of the committee through expedited procedures or referred to the full committee for review depending on the nature of the research.

Research Uses

Research uses of HESC lines must also be reviewed and approved by the HPSCRO Committee. Approval by other compliance committees may also be required as follows:

- *In vitro* HESC research with pre-existing HESC lines that are on the NIH registry
- *In vitro* HESC research with pre-existing HESC lines not on the NIH registry. These cell lines are not eligible for use in NIH funded research
- Research involving the introduction of HESCs or their derivatives into non-human or non-primate animals where the stem cells will not contribute to the central nervous system or germline (IACUC approval is required)
- Research in which personally identifiable information about donors of the blastocysts, gametes, or somatic cells from which the embryonic cells were derived is linked to the cell lines (IRB review is required)

HiPSCs

Derivation of HiPSCs from Tissue Outside of OU

IRB approval and informed consent are required for use of donor tissue for the derivation of HiPSCs. Tissue donated for derivation of HiPSCs from other institutions require a MTA and OU IBC approval prior to receipt of tissue at OU Researchers must submit an application to the HPSCRO Committee describing the plan for derivation of HiPSCs. The HPSCRO Committee will require submission of documentation that IRB approval and informed consent were properly obtained to procure the tissue. Once the consent process and plan for derivation of the HiPSCs have been deemed to be acceptable, the HPSCRO Committee will approve the application and the line derived from HiPSCs will be placed on the OU HPSCRO Committee internal registry.

Obtaining HiPSCs Derived Outside of OU

Researchers obtaining HiPSC lines from other institutions require a MTA and OU IBC approval prior to receipt of cell lines at OU. Researchers must submit an application to the HPSCRO Committee describing the proposed research uses of the cells. The HPSCRO Committee will require documentation that IRB approval and informed consent were properly obtained for derivation of the HiPSCs. Once verification that IRB approval and informed consent were properly obtained and use of the cells is permissible, the HPSRO Committee will approve the research and the HiPSC lines will be placed on the OU HPSCRO Committee internal registry.

Research Uses of HiPSCs

Use of HiPSCs in research also requires review and approval by the HPSCRO Committee. Depending on the nature of the research, review by other compliance committees may also be required. Permitted research uses of HiPSCs include the following:

- *In vitro* HiPSC research
- Research involving the introduction of HiPSCs into adult animals where the stem cells will not contribute to the central nervous system or germ line and animals will not be allowed to breed
- Research in which personally identifiable information about the donors of the tissues or somatic cells from which the HiPSCs were derived is linked to the cell lines

HPSRCO Committee Review

Applications should be submitted to the HPSCRO Committee for review. Submissions should include other approvals and applicable agreements. Review of HPSC research will be based upon the objectives and justification for use of HPSCs in research, cell line derivation, cell line provenance, and potential funding sources.

There are two processes by which HPSCRO Committee applications may be reviewed and approved. These include expedited review by the HPSCRO Committee Chair or another member of the committee designated by the Chair or review by the fully convened HPSRCO Committee. The type of review depends on the nature of the research.

Expedited Review by the HPSCRO Committee Chair or designated member of the HPSCRO Committee

Research proposals submitted for expedited review by the HPSCRO Committee should be submitted to the Director of Regulatory Support at sandborg@oakland.edu using the application found on the OU Regulatory Compliance web page. The HPSCRO Committee Chair or his/her designee will review the application to ensure the application falls within one of the permissible categories of expedited review and there are no ethical or scientific issues that must be addressed by the fully convened committee. Applications may be approved, require modifications, or referred to the full committee for review. Research which may not be approved will be referred to the fully convened committee for consideration and action. Researchers will be notified in writing within 7 calendar days of the review decision. Approval

is valid for a period of 3 years from the approval date. HPSCRO Committee approval is in addition to all other required OU compliance committee approvals (IACUC, IBC, IRB). Investigators may initiate all required approval processes in parallel following the submission guidelines of each compliance committee. However, research may not be initiated until the HPSCRO Committee receives approval letters from all other applicable compliance committees.

Once the HPSCRO application is approved, the research will be added into the HPSCRO Committee internal registry which captures all HPSC research conducted at OU. Regulatory compliance staff in the Research Office will maintain the registry.

Stem cell research eligible for expedited review and approval includes the following:

- *In vitro* HESC research with cell lines on the NIH Stem Cell Registry
- *In vitro* HESC research with cell lines not on the NIH Stem Cell Registry where appropriate IRB approval and informed consent can be verified
- *In vitro* HiPSC research where appropriate provenance, de-identification, and, if applicable, informed consent are verified
- Derivation of HiPSCs from donated tissue or somatic cells
- Introduction of HPSC derivatives (differentiated) into adult animals where the stem cells will not contribute to the central nervous system or germline and the animals would not be allowed to breed.

The HPSCRO Committee will be notified of all applications receiving expedited review and approval and placed on the HPSCRO Committee internal registry.

Proposed HPSC research that does not qualify for expedited review procedures will be reviewed at the next convened meeting of the HPSCRO Committee.

Convened Committee Review

Research proposals requiring full committee review must be submitted to the Director of Regulatory Support at sandborg@oakland.edu using the application found on the OU Regulatory Compliance web page. Applications will be reviewed by the HPSCRO Committee within 30 calendar days of submission. Applications may be approved, disapproved or require modifications. Applications may be tabled if the HPSCRO Committee finds that an application lacks sufficient information to make a determination. Researchers will be notified in writing within 7 calendar days of the committee's review decision. Applications may be approved for a period of 3 years. Approved research will be added to the HPSCRO Committee's internal registry. The committee must receive all other compliance committee approvals prior to the initiation of the research.

The committee shall meet on an ad hoc basis to review the following types of research:

- Research involving the introduction of HPSCs into non-human, non-primate animals at any stage of development
- Research in which the donors of the HESCs, tissues, human somatic cells or HiPSCs may be known or linked to the cell lines
- Derivation of HESCs

Impermissible HiPSC Research

Research that is not permissible regardless of the source of the HPSCs

- Research involving *in vitro* culture of any intact human embryo 14 days or older
- Research in which HPSCs are introduced into human blastocysts or non-human primate blastocysts

- Research involving the breeding of animals where the introduction of human pluripotent stem cells may contribute to the central nervous system or germ line.
- Derivation or research using HESCs from other sources including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes (or derivation of)

Continuing Review
Once approved, applications are considered active for a period of 3 years. Researchers are responsible for submitting a continuing review application to the HPSCRO Committee prior to expiration of the study. Continuing review applications can be found on the OU Regulatory Compliance webpage. Continuing review applications may be reviewed administratively or by the fully convened committee depending on the nature of the research.

Amendments
Researchers must receive prior approval of the HPSCRO Committee prior to making any changes in approved research by submitting an amendment form. Amendment forms can be found on the OU Regulatory compliance web page. Amendments to approved research may be reviewed administratively or by the fully convened committee depending on the nature of the research.

References
University of Michigan Policy on Research with Human Pluripotent Stem Cells including Embryonic Stem Cells and Induced Pluripotent Stem Cells

Wayne State University Human Pluripotent Stem Cell Research Oversight (HPSCRO) Committee Policy

University of Pittsburgh Policies and Procedures of the Human Stem Cell Research Oversight (hSCRO) Committee