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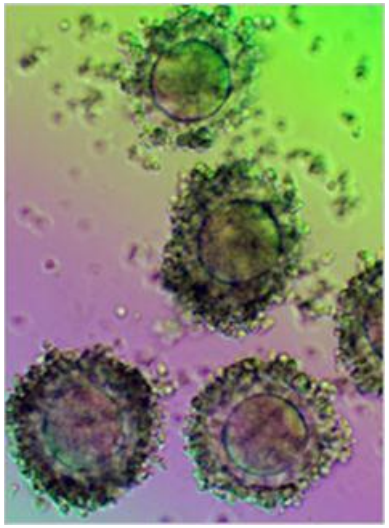

Human Stem Cell Compliance Tutorial

for human embryonic stem cell research and research using human induced pluripotent cells

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Stem Cell Research is conducted both at the UConn Health Center (UCHC) and the Storrs Campus (UConn)

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Human Stem Cell Research

There are six parts to this Tutorial:

1. **Role of the Stem Cell Research Oversight Committee in providing oversight of hESC and iPSC Research**
2. **Federal and State regulations**
3. **Responsibilities of the PI**
4. **SCRO and ORSP/OSP Forms**
5. **hESC research at another institution**
6. **Post-tutorial testing**

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Terms and Acronyms Used in this Tutorial

Human Embryonic Stem Cells (hESCs): hESCs are pluripotent stem cells that are self-replicating, derived from human embryos and are capable of developing into cells and tissues of three primary germ layers. Although hESC may be derived from embryos, stem cells are not themselves embryos.

hESC lines: A population of hESC that originated from a single hES cell.

hESC derivatives: Any partially differentiated cells obtained from hESC; DNA, RNA, proteins, or other products secreted or extracted from human embryonic stem cells.

Human induced Pluripotent Stem Cells (iPSCs): iPSCs are human pluripotent stem cells derived from non-embryonic sources through reverting somatic cells into an earlier stage of development.

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ROLE OF THE UNIVERSITY OF CONNECTICUT STEM CELL RESEARCH COMMITTEE

- The University of Connecticut Stem Cell Research Oversight (SCRO) Committee provides oversight on all ethical issues related to the derivation and research use of human stem cell lines at all schools, colleges, and research arms of the University of Connecticut regardless of the source of funding.

- The role of the SCRO Committee is to ensure that human embryonic stem cell (hESC) and human induced pluripotent stem cell (iPSC research is well-justified and that inappropriate and unethical research is not conducted.

- The ethical mandate of the SCRO Committee is to ensure that appropriate respect is given to the value of human life. It does so in part by evaluating risks to the value of human life and dignity in SCRO research against possible benefits to human health and well-being

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FOUNDATIONS OF THE ROLE OF THE SCRO COMMITTEE

- The review and approval of hESC research by a SCRO committee or its equivalent is required by the State of Connecticut.

- SCRO Committee review and approval of hESC research and some types of other pluripotent stem cell research is also required by the University of Connecticut's institutional policy.

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Scope of SCRO Oversight and Review

- **SCRO** reviews all proposals to derive or use human embryonic stem cells.
- **SCRO** reviews all proposals funded by the CT Stem Cell Research Fund, including those not using hESC lines.
- **SCRO** reviews induced pluripotent stem cell (iPSC) projects that transplant iPSCs or derivatives into prenatal animals or into the central nervous system of postnatal animals. It also reviews iPSC projects aimed at creating gametes.
- **SCRO** does not review derivation of new iPSC lines or *in vitro* iPSC research, unless funded by the CT Stem Cell Research Fund.
- Written **SCRO** approval is required before research within the scope of SCRO review may be conducted, and will be given only after documentation of other required approvals from the IBC, IACUC or IRB is received.
- See http://www.scro.uconn.edu for more information.

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SCRO Oversight

Four areas of hESC/iPSC where the SCRO has oversight:

1. All stem cell research using hESC lines and their derivatives
2. All research funded by the State of Connecticut Stem Cell Research Fund, including projects that do not use hESCs
2. All stem related to the creation and use of human embryos and gametes in hESC and iPS research
3. Generation and maintenance of human-animal chimeras in hESC and iPS research

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Use of hESC lines:

Investigators:

- Are authorized to use only the specified lines approved in their study.
- Must document procurement, culturing, storage, use, disposal, locations and user of hESCs in their possession.
- May not have a significant deviation in their SCRO protocol without SCRO approval.
- Should contact the SCRO before making any significant changes in goals or cell lines.
- Should remember that any modifications in research that requires IRB or IACUC approval must also be approved by the SCRO.

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Prohibited Activities

The following research activities are prohibited:

- *In vitro* culture of intact human embryos for longer than 14 days or past the formation of the primitive streak, whichever occurs first.
- Transfer of human embryo created by any method for research purposes into a human or non human uterus, particularly embryos created by nuclear transfer.
- Transplantation of hESC or hESC derivatives into a human blastocyst.

If any embryos are cultured *in vivo* past 14 days or the formation of the primitive streak, notify the SCRO Office and the Office of Research Compliance as soon as possible and follow standard disposal protocols immediately.

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Federal Guidelines for hESC Research

In July 2009 NIH adopted guidelines defining the eligibility of hESC lines for research with federal funding. These guidelines can be found at: http://www.stemcells.nih.gov/policy/2009guidelines.htm

Under the guidelines, hESC lines eligible for use with federal funding must meet the following conditions:

- Been derived from human embryos created for reproductive purposes that are no longer needed for this purpose;
- Donated by the individuals who sought reproductive treatment and gave voluntary written consent for their surplus embryos leftover from fertility treatment to be used for stem cell research;
- Documentation exists indicating that all options for future use of the surplus embryos were explained to the donors including donation for research, donation to another couple for reproductive use, storage of the embryos, and destruction of the surplus embryos.
- No payments, cash or in kind were offered for the donated embryos.
- The lines were reviewed and approved by the NIH Stem Cell Committee and placed on the NIH Human Embryonic Stem Cell Registry.

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Eligible and Ineligible Lines

Because of the federal funding directives, UConn has categorized hESC lines as:

1. **Eligible hESC lines:**
   Federal funds **may be used ONLY** for research using **eligible** hESC lines and their derivatives.

   Eligible hESC lines are those which have been reviewed and placed on the NIH Human Embryonic Stem Cell Registry.

2. **Ineligible hESC lines:**
   Ineligible hESC lines are those which have not been approved and placed on the NIH Human Embryonic Stem Cell Registry.

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Restrictions on the Use of Federal Funds

Federal funds **may not** be used directly or indirectly for research using ineligible hESC lines (or their derivatives)

Stem cell lines derived from embryos created for research purposes are ineligible for use with federal money.

Research to derive new hESC lines is also ineligible for use with federal money.

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Expendable Materials and Supplies

- Expendable materials and supplies in your current inventory that were purchased with federal funds may not be used to support in-eligible hESC research.
- New expendable materials and supplies for ineligible hESC research must be purchased with non-federal funds (gift, department or university research funds).

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State of Connecticut Legislation on hESC Research

- Connecticut is one of a several states that funds hESC research including ineligible hESC lines (i.e., research for which federal funds MAY NOT be used).

- Connecticut legislation established the **Connecticut Stem Cell Research Fund** in June 2005 from which $100 million for hESC research is to be disbursed over 10 years.

- Connecticut legislation established the **Stem Cell Research Advisory Committee** to oversee the distribution of funds and the **Stem Cell Peer Review Committee** to evaluate the scientific merit of grant proposals.

Cont.

State of Connecticut Legislation on hESC Research

- Conn. legislation does not allow payments to donors of human gametes and/or embryos for hESC research.
- A patient who donates embryos, gametes and/or embryonic stem cells for hESC research is required to provide a written consent for the donation under Connecticut law.
- Conn. law indicates that no person shall knowingly engage in the cloning of an individual, implant human embryos created by nuclear transfer into a uterus or facilitate human reproduction through clinical or other use of human embryos created by nuclear transfer.
- Derivation of hESC lines from embryos must occur before day 14 of embryo genesis or before gastrulation.
- Prior to initiating human embryonic stem cell research each PI must complete and sign the State of Connecticut Verification of Informed Consent which is to be filed with the Commissioner of Public Health.

State of Connecticut Legislation on hESC Research Cont.

- Persons who violate these provisions shall be fined and/or imprisoned.
- All hESC research conducted in the State of Connecticut must be reviewed and approved by a Stem Cell Research Oversight (SCRO) Committee that functions consistently with the National Academy of Sciences (NAS) Guidelines on human embryonic stem cell research as amended from time to time.
- A State of Connecticut Verification Form must be filed with the Commissioner of Public Health (DPH) for any stem cell research project that uses hES cells, human embryos or gametes. (The SCRO office forwards the completed form to DPH with the SCRO approval letter.)

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Role of the PI

Required To Implement and Follow Policies and Procedures:

- To ensure all faculty, staff, post-doctoral scholars, students, visiting scholars, and other researchers involved in your protocol working with hESC and iPCs are properly trained and are following institutional, state, and federal regulations.

- To ensure compliance with UConn federal and state policies, laws, regulations and guidelines.

- To submit the appropriate forms for review, continuation, amendments, or completion of SCRO protocols as required.

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Related Responsibilities of PI

- Initiate **SCRO Review.**
- Initiate **IRB, Animal Care, Radiation Safety and Bio-Safety Review** as necessary.
- Complete required **SCRO Compliance Tutorial.**
- Complete **SCRO and ORSP/OSP Forms** for all research projects and iPSC Research projects that fall within the mandate of the SCRO Committee, and all proposals funded by the Connecticut State Stem Cell Research Program funding.
- Complete a **Material Transfer Agreement Routing Form** for each hESC line requested.

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Starting the Project

Please provide the following documentation to the SCRO:

1. SCRO Protocol Application
2. Grant application if applicable
3. Completed State Verification Form
4. Compliance tutorial certificates for the PI and other staff members
5. As applicable, approvals or evidence of applications to the IBC, IACUC, and IRB

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SCRO and ORSP/OSP Forms

These forms must be completed for ALL research funded by the Connecticut Stem Cell Research Program and for all research that involves the use of hESC lines, human embryos, human gametes and creation of animal-human chimeras regardless of funding source - gifts, departmental funds, university research or externally funded grants and contracts.

In addition investigators must complete and submit SCRO forms for projects that transplant iPS or derivatives into the central nervous system of animals.

When Must the Forms Be Completed?

- Thirty days prior to the anticipated start date (for a gift, department or university research funded project);
- Complete an amendment form for changes in staff, research location, cell lines to be used, and significant changes to experiments.

SCRO CONTINUATIONS AND COMPLETIONS

SCRO Protocol Approvals are valid for one year. PI's must renew their protocols each year in order to be compliant.

When submitting your request for re-approval, please be sure to include any current committee approvals that pertain to your SCRO Protocol, such as IBC, IRB, and Animal Care.

All forms can be found by following this link:
http://scro.uconn.edu/forms.html

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Responsibilities of Relevant Institutional Committee & Offices

Stem Cell Research Oversight Committee (SCRO): Oversees all hESC research at UConn and some categories of iPSC research.

Institutional Review Board (IRB): Reviews hESC and IPSC research protocols that involve the use of human material with donor identifiable information and oversees donations of cells, gametes, and embryos to UConn researchers.

Office for Sponsored Programs (OSP) at Storrs or the **Office of Research and Sponsored Programs (ORSP)** at the Health Center: reviews and negotiates agreements for obtaining hESC and iPSC lines from other institutions.

Research Finance:

- Performs indirect cost calculation and verifies funding source of labs
- Reviews ownership and use restrictions for equipment in the proposed hESC research space.

The Animal Care Committee (ACC or IACUC)

SCRO review does not duplicate or replace any reviews by the **ACC** or **IBC** that are currently mandated by State, Federal, or Institutional policies or regulations.

Review by the **ACC or IACUC** is required for Stem Cell Protocols that:

- Implant human stem cells or progenitors into any nonhuman animal at any stage of the animal's development;
- Harvest any animal cells or gametes for use in human stem cell research.

- For **ACC/IACUC** information:
  UCHC: http://clacc.uchc.edu/Acc/AnimalCareCommittee.htm
  Storrs: http://iacuc.uconn.edu

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Institutional Biosafety Committee (IBC)

Review by the **IBC** is required for protocols that use recombinant DNA or any hazardous or toxic biological agents.

For **IBC** information:
UCHC: http://ors.uchc.edu/bio/biosaf1.html
Storrs: http://www.ibc.uconn.edu

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Facilities for hESC Research

Follow UConn's established Policies for Receiving Research Materials:

- Use the **ORSP/OSP Form** to list each lab, room, and office.
- This will alert **ORSP/OSP** to locate and identify all equipment that will be used and to research the funding of each facility for any federal contribution.
- Route the **ORSP/OSP Form** with the grant proposal to **ORSP/OSP.**
- Update and re-route the form **before** the project location changes.
- Researchers must take measures taken to ensure security and tracking.
- All labs in which hESC is conducted must comply at a minimum with BSL2 and blood borne pathogen standards.

UConn's established policies for obtaining research materials

All hESC lines require a **Material Transfer Agreement (MTA)** or similar agreement in place between the provider and UConn before hESC lines or iPS cell lines can be transferred to investigators.

1. Investigators requesting hESC lines from the UConn-Wesleyan Core should contact the Core to arrange for a Simple Letter of Agreement.

2. Investigators who wish to use hESC lines not obtained from the UConn-Wesleyan Core and who have received prior SCRO approval to use those cell lines should complete an MTA routing form and send it to the **Office of Research and Sponsored Programs (ORSP)** at UCHC or the **Office for Sponsored Programs (OSP)** at UConn.

3. **OSP/ORSP** will review the providers agreement for transferring hESC lines to ensure compliance with UConn policy, negotiate necessary changes, sign the agreement on behalf of UConn, and return the signed agreement to the provider, with a copy to the investigator.

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UConn's established policies for obtaining research materials cont.

4. OSP/ORSP will sign MTA agreements only after receipt of a copy of the SCRO approval.

5. For hESC lines not obtained from the Core, investigators must forward a copy of the MTA to the SCRO.

6. Investigators may not give hESC lines to other investigators who do not have an MTA for those lines.

7. Investigators may give hESC lines to other investigators who have the relevant MTA only with approval from the Core Director and the SCRO.

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Policy on Equipment Tagging

SCRO Policy with Regard to Equipment Tagging
February 27, 2013

It is the policy of the Federal Government that equipment and space funded under federal grants should be used solely for research with those human embryonic stem cell lines listed on the NIH Stem Cell Registry as lines eligible for use with federal grants. To implement this policy, the SCRO has mandated that all equipment and space used in hESC research be tagged so as to ensure that research with hESC lines not on the NIH Stem Cell Registry would not be used with equipment and rooms funded through grants from the federal government. Currently, very few University of Connecticut researchers are utilizing lines not on the NIH Stem Cell Registry. We are therefore refocusing the policy and no longer require all researchers to tag their equipment and space. Instead, we are only requiring that researchers using unapproved lines assume the responsibility to tag their equipment and space so as to preclude using federally supported equipment and space in the course of their research.

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hESC Laboratory Requirements

- All researchers must be Biosafety trained
- All researchers must be trained to handle hESC, human embryos and or gametes: the Uconn Stem Cell Core provides this training
- It is necessary to list all staff working on the protocol

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Conducting Research at Another Institution

There are at least three circumstances in which UCHC faculty can conduct research involving human embryonic stem cells at another institution. These include:

1) Being physically present at another institution.
2) Serving as a consultant for work at another institution.
3) Using eggs or embryos that were obtained from another institution.

Research Conducted at Another Institution

For UCHC faculty who are physically present at the host institution, go to: http://resadm.uchc.edu/hspo/investigators/index.html to download "Investigator's Guide for Human Subject Protections".

Because of the unique nature of research involving human embryonic stem cells, the following modifications and/or additions to your protocol are required:

- Like all projects involving human subjects, it is required that UConn faculty submit a UConn IRB application which includes any material submitted to another institution.

- To ensure compliance, the host institution must have Federal Wide Assurance that applies to all human subject research, regardless of funding source, or a letter must be provided from the host institution's IRB or like board stating that it will adhere to the rules that govern the UConn IRB.

- Research undertaken by a UConn faculty member must be conducted in accordance with the laws of the State of Connecticut.

- This policy also applies to those faculty members who choose to use their vacation time or take a leave to perform research at another institution if they intend to return to UConn.