# Massachusetts Institute of Technology
**Committee on Assessment of Biohazards**
**& Embryonic Stem Cell Research Oversight**

## Oversight Program for the Use of Biological Materials in Laboratory, Animal, and Human Research at MIT

## Scope, Policies, and Procedures

### I. Purpose and Objective of the Program

The Program for the oversight of biological research at MIT has been developed with two mutually supportive goals; ensuring the safe and responsible conduct of research and creating data-based policies and procedures through collaboration with the research community. The safe and responsible conduct of research is promoted by engaging investigators in the development of oversight policies and programs to ensure the health and safety of faculty, students and staff as well as protecting our surrounding community and the environment. The objective is the development of a coherent yet flexible compliance program that facilitates the transition of research from basic discovery in the laboratory, to studies in animals, to use in humans and possible clinically relevant therapies.

The program has two components, the Committee on Assessment of Biohazards and Embryonic Stem Cell Research Oversight (CAB/ESCRO) and the MIT EHS Biosafety Program (BSP). The CAB/ESCRO and EHS Biosafety Program work to develop mutually supportive policies and procedures with the Committee on Animal Care (CAC, the MIT Institutional Animal Care and Use Committee (IACUC)), the Committee on the Use of Humans as Experimental Subjects (COUHES, the MIT Institutional Review Board (IRB)), and the Office of the Vice President for Research to provide a comprehensive and cohesive research oversight process. The Managing Director of EHS and the chairs of the CAB/ESCRO, RPC, CTC, CAC and COUHES are voting members of the Institute Council on EHS (ICEHS) led by MIT's Vice President for Research. This active EHS Office engagement in these other Institute committees provides further support for our continuing effort to create a more comprehensive and effective oversight program.

### II. Authority and Responsibility of the CAB/ESCRO and BSP

a. CAB/ESCRO:

MIT established the Committee on Assessment of Biohazards (CAB), the MIT Institutional Biosafety Committee, in 1975 to comply with the newly created NIH *Guidelines on Research Involving Recombinant DNA Molecules*. The Biosafety Program (BSP) was established the same year and has been the operational support for the CAB research review and approval

process since its inception. The responsibilities of the CAB and BSP initially focused on recombinant DNA research, but have expanded over time to include:

- Research involving rDNA or synthetic nucleic acid technologies (including viral vectors)
- All uses of microorganisms
- Human and non-human primate (NHP) materials, cells, and tissues
- Human embryonic stem cells (hES cells) and induced pluripotent stem cells (iPS)
- Select agents and toxins
- Biological toxins
- Nanoparticle-based delivery systems for nucleic acids (information on nanoparticle generation shared with IH program)
- Use of any of the biological materials listed above in animals or humans
- All academic courses with laboratory components that utilize any of the biological materials listed above
- Dual Use Research of Concern (DURC) assessment

The purview of the committee was formally extended to include oversight of both hES and iPS cell-based research in September, 2005. The ESCRO designation was added at that time to indicate the extension of the committee's responsibilities. The committee extended its oversight to include synthetic biology in 2008.

The committee membership conforms to the requirements of the NIH Guidelines and the recommendations of the National Academy of Sciences. Information about CAB/ESCRO policies and procedures, and the research registration and review process can be found at the CAB/ESCRO web site (https://ehs.mit.edu/about/institute-committees/cab-escro-committee/). All necessary registration forms can be found via the CAB/ESCRO web page.

The CAB/ESCRO has established policies that promote the safe and responsible conduct of biological research. Specifically, the committee has established policies that:

- Ensure compliance with all applicable federal, state and local regulations through the institutional biological research registration and review process and the EHS Biosafety Program.
- Promote excellence in laboratory and research safety by actively soliciting and encouraging the involvement of the research community in the identification and development of best research practices, procedures and policies.
- Extend the scope of committee oversight to include all research involving the use of specified biological materials including developing new technologies as appropriate. This is done in concert with the VP for Research.
- Support the development and implementation of a wide-ranging education and training program for faculty, students, staff and employees to address the risks inherent in their work and research, and of appropriate safe practices, procedures, and containment measures.
- Support the development of an education and training program to enhance an understanding of new guidance on research biosecurity and management of dual use issues as they relate to life sciences research.

- Provide a clear review and approval process for research utilizing biological materials in laboratories and in animals.
- Provide clear guidelines for the appropriate containment levels for research materials that may be utilized in various teaching course laboratories, in laboratory and animal research, and in human subjects research.
- Promote adherence to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*; the Select Agent and Toxin regulations (42 CFR 73; 7 CFR 331; and 9 CFR 121); the CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories*; and other applicable standards.
- Promote the integration of oversight processes for research in the laboratory, animals and humans by collaborating with the CAC, COUHES, Division of Comparative Medicine (DCM), Radiation Protection Committee (RPC), and Committee on Toxic Chemicals (CTC).
- Establish a clear process for the oversight of research involving the derivation and use of human embryonic and induced pluripotent stem cells.
- Establish clear rules to prevent financial or ethical Conflict of Interest (COI) in all review and approval processes and policies pertaining to any research that falls within the purview of the committee.

To accomplish these ends the CAB/ESCRO will:

- Establish and maintain an oversight program that fulfills the stated goals of the program and ensures compliance with all relevant regulations and guidelines.
- Establish a broad definition of what constitutes biological materials-based research to include new and emerging areas as appropriate.
- Review all proposed biological research projects to promote the safe and responsible use of biological materials in research.
- Support the efforts of BSP to establish and maintain an extensive education/training program that meets the stated goals of the committee and complies with all applicable federal, state and local regulations and policies.
- Develop a consistent and data driven risk assessment paradigm to develop the appropriate containment measures for the use of biological materials in research laboratories, animals, and humans.
- Implement an appropriate oversight process for human embryonic stem (hES) and induced pluripotent stem (iPS) cell-based research.
- Review all teaching courses using biological materials to ensure safe practices and procedures and that the risks inherent in the proposed teaching laboratory projects do not exceed the research experience and expertise of the students.
- Establish the requirement that all biological research teaching laboratories implement an initial biosafety training or orientation for students.
- Establish the requirement that all biological research laboratories are inspected at least annually and that any deficiencies are resolved in a timely manner.
- Ensure that all personnel using biological material that falls within the purview of the committee receive the relevant biosafety training prior to working in a research laboratory.
- Support the integration of committee requirements and policies with the policies and procedures of the CAC, DCM, and COUHES.

- Maintain records of deliberations and actions taken at committee meetings and in the implementation of the oversight program.
- Submit all required compliance reports to federal, state, and local regulatory agencies in a timely manner.

b. BSP

The EHS Biosafety Program with the guidance of the CAB/ESCRO is responsible for the implementation of committee policies and procedures for the safe use of biological research materials in laboratories, animals, and humans. BSP collaborates with the CAC and DCM to ensure that appropriate biocontainment measures for research involving the use of biological materials in animals are supported and implemented appropriately. A similar collaborative effort is made with the COUHES to provide oversight for research involving the use of human materials, and when research involving the derivation of hES cells is proposed, or when investigators propose the use of biological materials in humans.

## III. CAB/ESCRO Biological Research Review and Approval Process

The review and approval process outlined below has been developed, assessed, revised and approved over a number of years. This process meets the requirements of all federal funding agencies. The three-year rewrite cycle, the requirement for annual renewal, and formal amendment procedure of the Biological Research Registration process are a balance between the committee's need to be up to date and informed about the ongoing biological research at MIT while not creating an undue paperwork burden on the investigators. The three-year rewrite cycle was chosen to coincide with the average length of both public and private research grants. Annual registration renewal review and approval are required for the continuation of research.

a. Initial Registration:

- All MIT investigators that wish to conduct biological research within the scope of the CAB/ESCRO must initiate the review and approval process by submitting a Biological Research Registration (BRR) draft to the MIT EHS Biosafety Program (BSP). The BSP conducts an independent internal review on the submitted draft, and investigators are expected to work with the BSP to complete the BRR document and address all questions and concerns before the document is placed on the agenda for the next CAB/ESCRO meeting.
- BL2+ Research: There are additional requirements for final approval for BL2+ research registrations, e.g. generation of a project specific manual, completion of project specific training, participation in any required Occupational Health and Surveillance program as requested by the CAB/ESCRO. The CAB/ESCRO reviews and approves all new BL2+ project specific manuals at duly constituted meetings. Additional requirements for BL2+ work are outlined in the CAB/ESCRO Policy #01: BL2+ Projects: Generic Requirements for Laboratory Facility and Biosafety Manual
- Human Embryonic Stem Cell (hES) Research: Investigators must submit a completed BRR form as well as an approved MIT COUHES protocol covering the

consent process for embryo donation before CAB/ESCRO review. All other COUHES approvals must also be in place prior to submission of the BRR to the CAB/ESCRO. The CAB/ESCRO review is the final step in the multi-committee approval process and must be obtained prior to initiation of the consent process of possible embryo donors. Additional information about the review and approval process for research involving human embryonic stem cells is described in Appendix A.

a. If non-NIH approved hES cell research is proposed the PI must indicate the source of non-federal funding, identify how the PI will ensure that non-NIH funds only will be used to support this research and how they will segregate that work. This must all be included along with the BRR. The EHS Biosafety Program will work with the investigator to ensure that the plan outlined for keeping work with non-NIH approved hES cells separate, is feasible and clear. BSP will check with the laboratory group periodically to see that the plan is functioning as intended.

- All new BRRs must have approval from the CAB/ESCRO before start of the activities described therein.
- Approved BRRs have an active period of 3 years contingent upon submission of an Annual Renewal.

b. Annual Renewal:

- Annual Renewals prompt investigators to review registered projects, review training records for project personnel, and to submit amendments as needed. The BSP reminds investigators about upcoming Annual Renewals and confirms that project personnel have completed the required biosafety training.
- Completed Annual Renewals are approved by the CAB/ESCRO Executive Secretary and are listed on the agenda for the next CAB/ESCRO meeting. Annual Renewals are subject to full committee review at any time.

c. Three-year Rewrite:

- At the end of the 3-year active period the investigator must submit a complete rewrite of their BRR that incorporates all the active projects and outlines proposed research for the next 3-year period. The rewrite should include a brief description of progress to date that incorporates a description of the goals and proposed research for the next 3 years. This will inform the committee and EHS Biosafety Program about possible directions and allow assessment of research and laboratory safety needs and identification of gaps. This is also important for forward planning for potential laboratory design changes, assessment of proposed animal research needs and containment levels, etc.

d. Extensions:

- An investigator's deadline for submission of a BRR annual renewal or a rewrite may under certain circumstances be extended to the next CAB/ESCRO meeting date after consultation with the Biosafety Officer or the committee Chairperson. This "extension" is meant to be a rare event. The BRR review timeline returns to its standard schedule for the next year so that the next review date would be in

less than 1 year. The Committee can grant further extensions based on specific requests.

Outside of the regularly scheduled registration updates, principal investigators may choose to take the following actions:

a. Amend:

- BRRs may be amended during the 3-year active period by submission of a completed amendment form describing the new research project for CAB/ESCRO approval.
- Amendments that fall **outside** the purview of the NIH Guidelines or that fall under section III-E or III-F of the NIH Guidelines, may be given administrative approval at the discretion of the Institutional Biosafety Officer. All administratively approved amendments are typically reviewed at the next CAB/ESCRO meeting, time permitting. If any questions or concerns arise at that time the PI must respond to all committee concerns.
- All amendments that fall under section III-A, B, C, or D of the NIH Guidelines cannot be administratively approved and must wait for the next duly constituted CAB/ESCRO meeting for approval prior to initiation of the work outlined in the amendment.
- The BRR must be amended to include all new hES cells.
- Research that must be conducted at BL2+ cannot proceed without full committee review and approval before initiation of the project. Investigators must meet all the requirements set forth in the committee's policy on BL2+ laboratories prior to initiation of the work. Amendments involving addition of personnel, use of new cell lines or tissues may be given administrative approval providing that all personnel trainings are up to date, that the cell lines and tissues are not known to contain bloodborne pathogens, do not contain rDNA/synthetic nucleic acids, and do not fall under the NIH Guidelines. All other amendments to research projects requiring BL2+ containment must be reviewed and approved at duly constituted CAB/ESCRO meetings.

b. Place on Hold

- A registration can be placed "**on hold**" if all biological research subject to CAB/ESCRO approval has currently ended but there may be the continuation of the work in the future. A hold is placed on a BRR by a formal request from the PI. No work shall be done on the project during the period of the hold. To remove the hold and resume work on the project, the PI is expected to complete a rewrite of the BRR, which is then submitted it to the CAB/ESCRO for review and approval before the "on hold" designation can be lifted.
- A BRR that is on hold is NOT approved and therefore no biological research subject to CAB/ESCRO approval may be conducted while the registration is on hold. Requirements for annual renewal of the registration are waived while a BRR is on hold; however, BSP staff will contact the PI each year to confirm that the registration shall remain on hold. To place a BRR on hold, using the BRR Renewal form is the preferred method. Alternatively, PIs can request to put their Registration on hold by email.

c. Change PI

- In some instances of a PI's leave or sabbatical, graduate students and/or postdoctoral investigators remain working in the laboratory. In most of these cases the PI is asked to identify another faculty member that will take responsibility for the remaining researchers and the registration covering the ongoing research. This is done by formal letter to the CAB/ESCRO to indicate that the on-site faculty member is now the PI and accepts responsibility for the remaining investigators, the laboratory and the ongoing research. This same process is followed if a faculty member moves to another institution and graduate students or postdoctoral researchers remain behind to finish up, or faculty are not present in the laboratory in cases of ill health etc.

d. Terminate

- If the biological research projects have ended, and the materials have been appropriately discarded or removed, a BRR will be terminated after the PI confirms that the work has ended, and the space is no longer to be used for biological research.

Most federal funding agencies and MIT RAS require documentation of institutional approval for biological based research outlined in grant submissions. At MIT this documentation is a CAB/ESCRO approval letter or email that has been sent within the last year.

Depending on the funding agency a Letter of Assurance of Compliance may be required. These are drafted for the Committee and signed by the Executive Secretary.

## IV. Membership of the CAB/ESCRO

a. CAB

The MIT CAB/ESCRO membership meets the requirements of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. The committee consists of at least 5 voting members. Members are recommended by the VP for Research, the Institutional Official (IO), and appointed by the President of MIT. The voting membership typically includes the following:

- Chairperson: a faculty member, because of the essential role of the CAB/ESCRO the Chair must be a full Professor with well recognized research expertise and experience.
- Other faculty members/ scientists, all actively engaged in biological research. Faculty members are selected to ensure that the range of knowledge and expertise of the members covers the breadth of biological materials-based research at MIT
- There are at least two community members not affiliated with MIT.
- One graduate student member recommended by the MIT Graduate Student Council.

- One postdoctoral researcher, a representative from the Postdoctoral Association.
- A member representing the MIT research technical staff.
- The Institutional Biosafety Officer, who serves as the contact for the committee, Executive Secretary of the CAB/ESCRO, and is an *ex officio* member.
- A senior member of Division of Comparative Medicine, a veterinarian with extensive animal research experience.

b. ESCRO

The review and approval process for research involving human embryonic stem cells is described in Appendix A. The membership of the committee is supplemented if asked to review biological research that involves human embryo donation and destruction for the derivation of human embryonic stem cells. These additional members allow the committee to fulfill its obligations as an ESCRO:

- an ethicist familiar with Massachusetts State and federal regulations concerning hES cell-based research.
- a board-certified physician with clinical experience in assisted reproductive technology and *in vitro* fertilization.

c. IRE

The CAB/ESCRO also serves as the IRE and reviews submission for Dual Use Research of Concern (DURC).

## V. CAB/ESCRO Meetings

- Meetings of the committee shall be in person, virtual (such as Zoom), or combination of the two.
- A quorum shall consist of a simple majority of the membership.
- Typically, meetings shall be held at least eight times a year with additional meetings arranged as needed. An agenda and materials to be discussed at the meetings will be distributed electronically for members to review materials prior to the meetings. Members may submit questions to the whole committee prior to the meetings for discussion or explanation during the meetings.
- Members of the public that wish to attend a meeting of the committee must contact the Institutional Biosafety Officer or the Chair of the committee. Members of the public that do attend will only be invited to make a comment at the end of the meeting. Members of the public that do attend may not question members of the committee during the comment time.
- Minutes of the meetings may be obtained by members of the public by request to either the Institutional Biosafety Officer or the committee Chairperson.
- Approval of registrations and issues considered by the CAB/ESCRO during its meetings shall require a majority vote of those attending that meeting.
- All minority opinions are considered and are noted in the minutes.

- Investigators may be invited to attend meetings or give presentations to assist the committee in protocol review and assessment or to introduce new technologies to the committee.
- Minutes are taken at each meeting and included in the next meeting packet for committee approval. Minutes will summarize discussions and clearly indicate committee decisions but will not contain specific attributions or locations of research.
- Where the members of the public request copies of committee meeting minutes, all minutes will be reviewed prior to release to ensure that locations of the research laboratories, and information about specific types of research (involving use of animals, related to locations of select agents and toxins, or locations of research) are not present. PI office locations will also be removed prior to release into the public domain. As far as possible comments and questions arising during the meeting will not be attributed to individuals. Redacted minutes with follow the requirements of the NIH Guidelines. As an informal policy, the redacted minutes are provided within 20-25 working days depending on the number of meeting minutes covered by the request. The Institutional Biosafety Officer informs the committee Chair and members and the IO when FOIA requests are received. Depending upon the request it may be prudent to inform NIH OSP of the request as well.

## VI. CAB/ESCRO Decisions

The committee may vote to “Approve”, “Approve pending modifications”, “Approve with Stipulations”, or “Not Approved”.

- A vote to “**Approve**” means that the information in the registration was considered clear and adequate and once a formal approval letter has been sent the investigator may initiate the research project as described.
- An “**Approval pending modifications**” means that the committee finds the registration generally acceptable and will approve it when specific questions are answered, or items clarified.
- An “**Approval with Stipulation(s)**” means that the research may start but the committee placed a specific requirement that must be fulfilled or adhered to as part of the conduct of the research. These stipulations can be a request for data submission from small preliminary experiments where the risk and appropriate containment measures are not clear, or the use of specific safety equipment, etc. The stipulation is discussed with the investigator to ensure complete understanding and assist the PI in fulfilling the committee’s requirement. If data has been requested this is provided to the committee for review at the next meeting. The provision of the data and committee assessment of the data is noted in the meeting minutes. The stipulations are also outlined in the approval letter. BSP staff periodically visit the laboratory to be sure that the committee requests/stipulations continue to be implemented.
- A vote to “**Not Approve**” means that the committee has serious reservations about the safety of the research. The investigator will be asked to submit a rewritten registration that addresses all the concerns of the committee if the PI wishes to pursue that line of research. The investigator may be invited to attend

the next committee meeting to discuss the research and appropriate containment measures. A vote to "Not Approve" is very unusual. The internal BSP review process attempts to detect issues that make a research project too risky to proceed either due to risks inherent in a specified biological agent or materials, lack of appropriate research containment space or safety containment equipment, or lack of appropriate research experience. When these issues arise BSP staff attempts to work with the PI to address them and/or modify the research long before a registration document is considered ready to be placed on the CAB/ESCRO meeting agenda.

- Where high risk research is proposed the committee often invites the PI to a meeting so that a direct question and answer exchange can occur. In some instances, investigators are asked to conduct small exploratory experiments to generate data addressing the committee's concerns and safety issues with the understanding that the resulting data will be sent to the CAB/ESCRO. The investigator may be invited to attend the meeting to discuss the results from these preliminary experiments. The intent is that following the discussion and review of data the committee will be able to establish appropriate containment measures. Once the committee members decide that all questions and concerns have been addressed and have agreed upon the appropriate containment level a motion to approve can be made. If a majority agrees, a formal approval letter that covers the full scope of the research outlined in the biological research registration is sent to the PI. Conversely, if the information or data is considered equivocal or insufficient, the investigator will be asked for additional experimental data and the experimental design will be assessed. These data assessment and discussions may be done only at full committee meetings.
- Investigators are informed of all committee decisions by formal letter or email. Approval letters can be copied to departmental Chairs/Directors or Administrative Officers, OSP, funding agencies, etc., as needed or requested. A "cc" list is maintained within BSP for each Department, Laboratory, and Center that is tailored by the Department, Laboratory or Center to suit their needs.

## VII. Conflict of Interest

Where a committee member has a conflict of interest (COI), financial or ethical, the member is expected to make that conflict clear to the Chair prior to review and discussion of any research registration. The Chair will decide the appropriate steps to remove that conflict. If there is some doubt about the proper course of action, the Chair and the Biosafety Officer may discuss the issue with a variety of resources within MIT including the Office of the General Counsel. Depending on the outcome of that discussion, the Chair and BSO may inform the committee of the potential COI so that the committee understands that the investigator must recuse themselves from the discussion as well as the approval vote. Where the conflict is one of financial interest the committee may ask for some clarification of the financial relationship of the investigator and how this relates to the research to be conducted at MIT and whether this will involve the use of MIT resources for financial gain.

Where a CAB/ESCRO member is a PI on a research registration the member must abstain from voting on the registration but may answer questions during discussion. As appropriate, the

Chair may request that the member leave the room during the committee final discussion and vote. The member may return to the room once the vote has been recorded in the minutes. However, if the other members of the committee have no questions about the research registration, the member must abstain from voting, but the Chair may decide that it is not necessary for the member to leave the room during the committee vote.

## VIII. CAB/ESCRO: Research Materials, Laboratory Design, and Safety Recommendations and Policies

The CAB/ESCRO makes recommendations and has policies in place aimed at reducing research risks and clarifying containment levels for various types of research materials and for the design and the safe conduct of research.

a. Recommendations on Research Materials

- Where possible, human and NHP established cell lines should be obtained from sources that are able to provide data showing that the cell line is free of standard viral and bacterial pathogens consistent with the OSHA BBP standard and that have been authenticated as human or nonhuman primate and without cross contamination. Examples of such sources include American Type Culture Collection (ATCC), *Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH* (DSMZ, www.dsmz.de), and Nonhuman Primate Reagent Resource. These repositories provide tested and well characterized human and NHP cell lines. Investigators must make it clear if they wish to use cell lines that are known to carry a particular naturally occurring virus, for example a human liver tumor cell line that is positive for HBV genome. In these instances, further information would be needed to understand whether viral genes are expressed (viral RNA detected and protein antigens identified) before acquisition and use of the cell line.
- Where investigators wish to use known drug-resistant variants of human or animal pathogens the investigator must provide BSP with information about the drug sensitivity pattern of the proposed drug-resistant strain. This sensitivity information must include both first and secondary drugs that remain as therapeutic options. This is requested since it is important to be clear about therapeutic options available in case of exposure or injury. If the list of effective drugs is short, then BSP and the committee will request further information on why the research cannot be done with a strain that is resistant to only one drug. The committee decides to allow or not allow the use of a multidrug resistant strain. The list of therapeutic options is retained in the laboratory so that it might be taken to MIT Health in case of an exposure/injury. A copy is retained in the investigator's BRR and reviewed annually as part of the standard research review and approval process.

b. Policies on Research Material Characterization

- **Human cell lines** must be tested and shown to be free of a standard panel of zoonotic agents prior to use in animals (CAC policy). See above as well.

- **Gene transfer viral vectors** should be tested in accordance with CAB ESCRO Policy 06 – Lentiviral Vector Testing for Replication Competence.
- **Verification of attenuation of high consequence microbial agent strains**. Investigators must have data either generated in their laboratory or provided by the supplier sending the agent showing the expected attenuation, or lack of viability, is present in the particular strain or treated culture before the agent may be used at a lower containment level. See CAB ESCRO Policy 04 – Attenuated Strain Verification.
- **Additional committee policies** that deal with various laboratory safety and security measures are available via the CAB/ESCRO web page.
- **Review of Laboratory Incidents:** the EHS Biosafety program investigates laboratory associated incidents involving all biological research materials. The objective is to identify the cause of the exposure and develop/recommend preventive measures in collaboration with the researchers. Incidents can be discussed at CAB/ESCRO meetings with the goal of identifying systematic issues that could be leading to incidents where a committee policy might prove useful in driving a solution.

## IX. Review and Approval Process: the role of BSP

A detailed description of the CAB/ESCRO review and approval process can be found in Section III of this document. The EHS Biosafety Program serves as the operational arm of this process.

- BSP makes every effort to have new Faculty submit a Biological Research Registration for CAB/ESCRO review **well before they arrive at MIT**. While their research may not start until their laboratory is finished, and MIT training completed, having early committee review and approval of the research makes the faculty member's transition to MIT significantly easier. This allows BSP to assist the PI in many more areas, such as with renovation of research space, and serves as an early introduction to the review and approval process. It also gives new PIs a known contact to use to help them make the transition to the area. BSP identifies faculty members that use biological materials in their research in a variety of ways; through interactions with RAS, AOs, or DLC EHS Coordinators. In some cases, investigators have been identified by their webpage research descriptions. The members of the Biosafety Program make an effort to understand new faculty research areas in order to assist with the registration process and laboratory renovations.
- Faculty members are sent the latest version of the BRR form by email, or they may download the form from the CAB/ESCRO website
- Faculty members collaborate with a designated BSP staff member to complete a draft BRR form that meets the approval of the PI and the Biosafety staff person.
- The draft BRR is reviewed by BSP staff with the final review by the Institutional Biosafety Officer. During this internal review all questions and comments are entered on an internal review tracking sheet. The questions and comments about the BRR are returned to the staff member and are communicated to the PI for response and modification of the BRR as needed. The review tracking sheets are retained to document the internal review process and to ensure that questions and comments are addressed.

- The Biosafety staff person works with the PI to develop a clear and focused response to all questions. Particular attention is paid to assays associated with agent virulence, host range, replication defects, antibiotic resistance patterns.
- During the internal review process any concerns about laboratory design and safety features of the research facility are identified, and the PI and Facility Manager are contacted for clarification and discussion. Any plans for renovation are reviewed and comments sent to the PI, Project Manager, and architect. If no renovations are needed, the laboratory is inspected; the EHS Management System data entries such as training records, space registration and room hazard lists are reviewed for accuracy; and where needed investigators are referred to Occupational Health for assessment and/or offer of a vaccine. All training needs assessments and trainings should be completed, or training sessions arranged prior to CAB/ESCRO consideration of the new BRR.
- During the review process, PIs are referred to CAC and COUHES as needed. Issues involving the other institutional committees should be addressed or in the process of being resolved before the BRR proceeds through the CAB/ESCRO review process.
- Once all questions or issues have been resolved to the satisfaction of the various stakeholders, the new registration is added to the CAB/ESCRO agenda for the next meeting.
- All BRR are reviewed by the CAB/ESCRO. Once the committee has approved the research registration a formal letter of committee approval is sent. This letter also outlines that the research may not start until laboratory renovation is completed, the facility inspected, and trainings are done.
- Where a registration is not approved, the investigator may meet with the Biosafety Officer to clarify the issues. If the issues can be resolved, the Biosafety Officer will assist the PI in submitting a revised BRR form that addresses the issues raised by the committee.
- There is a simple post-approval monitoring process for labs engaged in biological research. After CAB/ESCRO approval, Biosafety staff remain in contact with research laboratories through a variety of means to ensure that safe practices and procedures are being followed, that if changes in the research are planned, the BRR is amended in a timely manner, that training and safety issues are addressed in an ongoing manner, that the registration document and CAB/ESCRO review and approval has been done for all ongoing work.
- BSP staff members are encouraged to attend lab group meetings to conduct trainings so that any questions or concerns can be heard and discussed, and if needed, answers or solutions found and implemented. The objective is to be able to provide as much help or assistance for the safe and responsible conduct of research as is needed without creating additional layers of oversight or bureaucracy.

## X. CAB/ESCRO Permits and Reporting Requirements

a. CAB

- The Committee is required to submit an annual compliance report to the NIH Office of Science Policy (NIH OSP) as required by the NIH Guidelines. An NIH OSP notice via email confirming compliance is kept on file in the EHS BSP office.

- The Committee submits an annual compliance report to the City of Cambridge Biosafety Committee (CBC) as required by local regulation (Chapter 8.20 of the Cambridge Municipal Code). This report is submitted every January.
- MIT is registered with the City of Cambridge and the CBC and maintains a permit to conduct rDNA-based research in the City of Cambridge. This permit is renewed annually for a fee. The City of Cambridge sends an annual bill to the EHS Biosafety Program. The cost of the permit is based on square feet of research space. An estimate of the amount of research space can be found via the Provost's Office.
- Reports of incidents and accidents involving rDNA or synthetic nucleic acids and or microbes containing rDNA or synthetic nucleic acids are sent to NIH OSP and the City of Cambridge Biosafety Committee in accordance with the NIH Guidelines.
- Within MIT the CAB/ESCRO reports directly to the Vice President for Research. Copies of reports to outside compliance agencies are sent to the VP for Research
- Copies of all reports are kept in the EHS office in the CAB/ESCRO correspondence file.
- Permits are kept as separate files by responsible agency.

b. ESCRO

- The Committee submits an annual report to the State of Massachusetts Executive Office of Health and Human Services, Dept of Public Health on research based on use of human embryonic stem cells (hES cells). The State DPH required permit to conduct hES cell-based research is renewed every 3 years.

## XI. Document Retention and Archiving: Biological Research Registrations, OSHA Exposure Control Plans, Permits & Licenses, Letter of Assurance, etc.

a. Biological Research Registrations

- Access to all files is limited to BSP staff as much as possible (information technology staff might have access for maintenance of systems.)
- Electronic versions of all approved Biological Research Registrations, amendments, rewrites, annual renewals, and approval letters are maintained in the Biosafety office for at least 5 years.
- Paper/hard copies of all BRRs, electronic copies of approval letters, requests for information, relevant publications are kept in the Biosafety office for at least 5 years. After that time the paper copies are archived. Archived materials are retained for at least 30 years.

b. DCM Forms

- Copies of animal research biosafety assessment forms are held on file like the PI's BRR.

c. Exposure Control Plans

- Electronic and paper copies of these plans are retained for at least 5 years.
- Training signature pages, training data, and documentation of HBV vaccination offers or declinations are retained as required by the OSHA BBP standard.

d. Permits and Licenses

- Copies of all permits and licenses are held for at least 5 years.
- Beyond that time, scanned electronic copies are retained for at least 10 years.

e. Letters of Assurance

- Letters of assurance for investigators are retained in their BRR file and the same timeline is followed as for the BRR.
- Institution wide letters of compliance or assurance are held in separate files by requesting entity. These are retained indefinitely.

## XII. Integration of CAB/ESCRO Oversight with CAC and COUHES

a. Committee on Animal Care (CAC)

- There are several areas of mutual responsibility between the CAB/ESCRO and the CAC; ensuring the health and safety of researchers working with animals and Animal Care staff engaged in the care and handling of animals that have been exposed to biohazardous materials.
- The CAB/ESCRO has established the appropriate biocontainment level for the use of various biological materials in animal research including human primary and established cells and materials, viral vectors, and pathogens. The objective of the policy outlining the appropriate biocontainment level and safety practices and procedures is to prevent animal to animal, animal to human, human to human, and human to animal transmission of any infectious agent.
- Investigators are responsible for obtaining all required approvals for every Committee having purview over the research.

b. Committee on Use of Humans as Experimental Subjects (COUHES)

- If a biosafety issue arises as part of a human research proposal the BSO is able to provide advice or helps seek adequate expert opinion on patient and researcher safety, infection control, as well as inclusion of adequate information and language in the Informed Consent document.

## XIII. Other oversight activities of the CAB/ESCRO

- MIT laboratories and facilities where biological research is conducted or taught are inspected at least once per year by a member of the BSP representing the EHS Office and the CAB/ESCRO.
- All reports of governmental agencies conducting official visits or inspections at MIT laboratories or research facilities should be mentioned to the CAB/ESCRO at its regular meetings

- All reports of significant biological research laboratory incident or spill shall be presented to the CAB/ESCRO at its regular meeting. BSP staff work with the PI to implement any CAB/ESCRO recommendations after review of the circumstances of the incident or spill
- The CAB/ESCRO may ask for follow up on any report at any time to ensure that the root cause of an incident has been identified, or a finding has been corrected.
- Where the incident involves a possible exposure to recombinant DNA or synthetic nucleic acids materials or agents containing recombinant DNA or synthetic nucleic acids the Biosafety Officer will report the incident to NIH OSP, the City of Cambridge Biosafety Committee and the Chair of the CAB/ESCRO within 30 days of receipt of the report or notification. The 30 days reporting time will give the Biosafety staff time to investigate the incident. If the incident requires additional information or follow up a final letter will be sent to NIH OSP and the City of Cambridge Biosafety Committee outlining subsequent findings and conclusions. Incidents involving exposures are discussed at CAB/ESCRO meetings with the goal of identifying areas where committee policies may be developed that address issues contributing to laboratory accidents or incidents.

## XIV. Educational Activities of the CAB/ESCRO

- The CAB/ESCRO will establish the minimum training needs for all biological research based on the risks inherent in the research and the experience level of the investigators.
- The training will be conducted by BSP staff or other proficient individuals, as approved by BSP.
- Biosafety Program staff develop training programs for faculty, students and staff, aimed at addressing the risks of biological research and new and emerging technologies in use or being developed at MIT. The training for staff such as Campus Police, Facilities repair and maintenance personnel and custodial staff (non-research members of our community) focuses on how to do their jobs safely in research labs and animal facilities, whom to contact before entering research areas and what not to touch, what to do in case of injury or an incident, and the constant offer of HBV vaccinations.
- The committee may be asked to review training program content as needed, to ensure that it is designed to promote safety and a culture of responsibility
- The committee requires that the training program include teaching of state, municipal, institutional, and federal rules, regulations and guidelines
- The CAB/ESCRO committee has developed special guidelines, registration questions, and training requirements for teaching laboratories including biosafety training and the need for a high ratio of graduate teaching assistants to student ratio in these labs. These policies are aimed at ensuring that the research conducted by undergraduates does not pose a risk to the students due to their lack of expertise and laboratory experience.
- In an effort to support the Undergraduate Research Opportunity Program and maintain the ability of experienced undergraduates to safely conduct independent research the committee has developed a policy that allows experienced students to work unsupervised and out of hours with the specific written permission of the PI.

The PI and undergraduate create a clear description of the research that can be done unsupervised and out of hours, outlines what to do in case of an incident, how to get help if needed. This is signed by both parties and sent to the Biosafety Program. It is filed with the PIs BRR.

## XV. Limits of Purview and Authority

a. Intramural Research

- CAB/ESCRO oversight shall be confined to those research laboratories and personnel working in those research labs in facilities owned and or operated by MIT. Biological research is defined as the research use of rDNA or synthetic biology technologies, pathogens, microbial agents, biological toxins, human and NHP materials, hES cells, iPS cells, or nanomaterials in the laboratory, in animals or in humans.
- Facilities or entities that conduct biological research, that are affiliated with MIT yet are not located on the main MIT campus, fall within the aegis of the CAB/ESCRO and Biosafety Program purview and authority. Examples of these facilities include Lincoln Laboratory, Bates LINAC, Haystack, and the MIT Reactor.
- When biological research is conducted at MIT by persons not affiliated with MIT, this research must be registered with the Biosafety Program and CAB/ESCRO. An MIT faculty must be considered the “Principal Investigator” and shall assume “sponsorship” of those persons and co-sign requests for research approval and biological research registrations. Co-signed BRRs by such unaffiliated persons shall be processed as intramural registrations and requests for approvals.
- The CAB/ESCRO has authority over the use of biological materials for teaching purposes sponsored by MIT regardless of where that teaching is undertaken.

b. Extramural Research

- When research involving the use of biological materials is funded entirely through another institution, but a portion or all of the work is conducted at MIT, the CAB/ESCRO shall assume the usual obligations including review and approval of the BRR application and shall ask for confirmation of approval by the IBC of the other institution in writing. The BRR submitted for CAB/ESCRO review shall clearly delineate the work conducted at MIT and if any materials/equipment/ personnel exchange is part of the collaboration.
- When research involving biological materials is performed entirely through another institution and the collaboration with MIT does not demand that any portion of the work occur at MIT, the CAB/ESCRO may accept the approval of a similar committee of the other institution without further review. The CAB/ESCRO may choose to document the work. The CAB/ESCRO may ask for periodic updates to apprise the committee of the status of the research, whether any incidents or spills occurred, and the training received by MIT affiliated personnel. Administrative oversight of these research activities involving MIT personnel is not precluded by the conduct of the research off site.

## XVI. References:


1. Department of Health and Human Services, National Institutes of Health. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.
2. CDC/NIH. Biosafety in Microbiological and Biomedical Laboratories.
3. NRC. Guide for the Care and Use of Laboratory Animals.
4. Select Agent and Toxin regulations (42 CFR 73; 7 CFR 331; and 9 CFR 121)
5. National Science Advisory Board on Biosecurity (NSABB) Guidance on Synthetic Biology, Biosecurity and Dual Use Research.
6. National Research Council, Institute of Medicine, National Academy Guidelines for Human Embryonic Stem Cell Research.
7. Chapter 8.20 of the Cambridge Municipal Code.

## Appendix A: Review and Approval Process for hES Cell-Based Research

### Role of the MIT Committee on Assessment of Biohazards/Embryonic Stem Cell Research Oversight and Interaction with the IACUC (Animal Care and Use), and COUHES (Human Subjects Protection) in oversight of hES cell research

The National Academy of Sciences has recently published guidelines for the oversight of research involving human embryonic stem cells (www.nationalacademies.org). These guidelines recommend that institutions or entities form an Embryonic Stem Cell Research Oversight (ESCRO) Committee with specific expertise if investigators plan on conducting research involving the generation or use of human embryonic stem (hES) cell lines. The ESCRO committee would be charged with the review and approval of research involving hES cells and with ensuring that the NAS recommendations and OHRP requirements for informed consent for donation of human materials were fulfilled.

At MIT the Committee on Assessment of Biohazards (CAB) reviews and approves research utilizing human materials. The CAB voted to extend its purview in 2005 to include hES cell-based research with the approval of MIT Academic Council. The committee extended its name to become the CAB/ESCRO to reflect this additional responsibility.

MIT has developed a multi-level oversight process for research involving hES cells that provides increasing level of scrutiny for research beginning with research utilizing federally approved hES cells, the next level deals with use of pre-existing hES cell lines that are not federally approved, with the highest-level oversight for the derivation of new hES cell lines. Where investigators propose to derive new hES cell lines additional experts attend the CAB/ESCRO meetings to review the proposed research, address any ethical issues and ensure compliance with OHRP requirements (Table 1).

Where investigators propose the use of federally approved pre-existing hES cell lines, the oversight process requires that the PI identify and document the source of the hES cell line and complete the registration and approval of the research following the usual CAB/ESCRO process. If the research involves use of pre-existing but not federally approved hES cell lines, the investigator must provide the identification or designation of the cell line(s) to be used, identify the source of the cell lines whether it is another investigator or a commercial source, as well as provide the CAB/ESCRO with written assurance that the derivation and donor consent process was reviewed and approved by a federally registered IRB. Where investigators wish to derive new hES cell lines additional members with specific expertise augment the CAB/ESCRO review process.

**Table 1. Outline of Oversight Levels and Components**

| Level of Oversight [1] | hES cells [2] | Laboratory Use | CAC | COUHES |
|---|---|---|---|---|
| Level I<br><br>***Research falls within standard CAB/ESCRO registration & approval process with additional documentation needed as outlined*** | Research involves pre-existing hES cell lines | CAB/ESCRO has purview:<br>(a) Standard BRR review and approval process to be followed;<br>(b) CAB/ESCRO approval required prior to initiation of laboratory use of hES cells.<br>(c) provenance[3] of cell line required as part of research registration;<br>(d) if non-NIH registered cell line is to be used then assurance of non-federal source of funding for support of all research involving cell line must be provided [4] . In addition letter assuring that donor consent process was reviewed and approved by a federally registered IRB accompanies the BRR. | N/A | N/A |
| **Level II**<br><br>***All uses of any hES cells or adult human stem cells in animals (pre or post-natal injections)*** | Established hES cells or adult stem cells | CAB/ESCRO and Biosafety review & approval for proposed research for standard studies. | N/A | N/A |
| | | CAB/ESCRO, Biosafety and IACUC special attention where use in animals involves hES cell research that might result in acquisition of more "human" traits or characteristics (e.g. injection of hES or adult human stem cells to animal brain or chimeric animal created). | Review & approval by CAC prior to final CAB/ESCRO approval. All approvals must be in place prior to initiation of animal research. Documentation of animal sacrifice at end of experiment sent to CAB/ESCRO. | |

| | | | | |
|---|---|---|---|---|
| **Level III** [5]<br><br>***CAB/ESCRO plus additional experts must review & approve proposed research, additional documentation plus letter of approval for consent forms and process from COUHES.***<br><br>***COUHES approval letter stating that signed consent forms on file with CAB/ESCRO, etc.*** | Derivation of **new** hES cell lines from donated blastocysts, in vitro fertilized oocytes, or by nuclear transfer | CAB/ESCRO has final approval & oversight.<br>(a) CAB/ESCRO must review & approve the scientific rational for the need to generate new hES cell lines,<br>(b) including justification for the number of blastocysts and oocytes requested;<br>(c) documentation of COUHES approval of the procurement process must be presented;<br>(d) if research could result in identifiable information about donor then investigator must also outline privacy protection measures;<br>(e) where FDA regulations are applicable PI must ensure confidentiality & that donors are aware that cell line traceability will be maintained | See Level II | Investigator must register with MIT COUHES.<br>COUHES must review & approve consent form and process; ensure all donors have assented before blastocysts or oocytes are released; ensure HIPPA regulations and concerns are addressed.<br>PI must supply letter of approval from COUHES to CAB/ESCRO. |
| **Level IV:**<br><br>***Experiments that will not be approved*** | 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 is NOT permitted.<br><br>hES/adult stem cells may NOT be introduced into human blastocysts.<br><br>Research in which hES/adult stem cells are introduced into nonhuman primate blastocysts is NOT permitted.<br><br>No animal into which hES/adult stem cells have been introduced at any stage of development will be allowed to breed.<br><br>hES/adult stem cells may NOT be introduced into human blastocysts. | | | |

1. CAB/ESCRO membership plus additional expert members for review of Level II and Level III research.
2. All hES cell lines used at MIT should be pre-coded or anonymous. Various commercial vendors of NIH approved hES cell lines do not have nor request personal information about donor source
3. Provenance or documentation should include evidence that the procurement process was approved by an Institutional Review Board to ensure adherence to the basic legal and ethical principles of informed consent and protection of confidentiality.
4. Where non-NIH approved hES cell lines will be used PI must establish some mechanism to ensure that no federal monies are used to support the research involving these lines. This includes things such as no sharing or use of equipment, spaces, supplies purchased with federal funds; portioning and accounting of employee time and salaries that must come from non-federal sources. Investigators must be able to show that all equipment, etc used in research involving these non-NIH approved hES cells utilizes NO federal monies in any way.
5. Small research animals such as mice, rats, rabbits, gerbils only. Injection of hES cells into non-human primates is not permitted. No animal that has received hES cells will be allowed to breed. All hES cell recipient animals will be sacrificed at the end of the experiment.