

Welcome to the 2016 Summer Edition of the IACUC Connection, a quarterly newsletter designed to help researchers with questions regarding animal research at UConn Health. This issue is going to revisit the regulations involving recombinant or synthetic nucleic acid molecule research.

Federal Regulations – Recombinant DNA Work

All work with recombinant or synthetic nucleic acids molecules must adhere to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* ([NIH Guidelines](#)). This federal guideline can be found on the IACUC website, the EH&S website, and can also be found at the following web link: <http://osp.od.nih.gov/office-biotechnology-activities/rac/guidelines/guidelines.html>. When institutions receive NIH funding for research involving recombinant or synthetic nucleic acid (r/s NA) molecules, they must follow the provisions for containment and biosafety oversight set forth in the [NIH Guidelines](#). Compliance with the [NIH Guidelines](#) is mandatory; failure to adhere to the [NIH Guidelines](#) can result in suspension or termination of NIH funding for this type of research or lead to a requirement for prior NIH approval of any or all r/s NA molecules projects at the institution. Compliance with the [NIH Guidelines](#) is critical to the safe conduct of research and to the fulfillment of an institutional commitment to the protection of staff, the environment, and public health.

Federal Regulations – Definition of Recombinant DNA

In the context of the [NIH Guidelines](#), recombinant and synthetic nucleic acids are defined as:

- (i) Molecules that
 - a. Are constructed by joining nucleic acid molecules; and
 - b. Can replicate in a living cell, i.e., recombinant nucleic acids;
- (ii) Nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or
- (iii) Molecules that result from the replication of those described in (i) or (ii) above.

Applicability of the [NIH Guidelines](#)

The [NIH Guidelines](#) are applicable to:

1. All recombinant or synthetic nucleic acid research within the United States where research is conducted at, or sponsored by, an institution that receives any support for recombinant or synthetic nucleic acid research from NIH.
2. Research that involves testing in humans of materials containing recombinant or synthetic nucleic acids developed with NIH funds.

It is a condition for NIH funding of recombinant or synthetic nucleic acid molecule research that institutions ensure that such research conducted at, or sponsored by, the institution – irrespective of the source of funding – shall comply with the [NIH Guidelines](#). This means that even if your research is not funded by NIH, **you must still comply** with the [NIH Guidelines](#) because UConn Health receives NIH funding for other research.

Categories of Experiments Covered by the [NIH Guidelines](#)

The [NIH Guidelines](#) has established six categories of experiments utilizing rDNA:

III A: Requires IBC approval, RAC review, and NIH Director approval prior to initiation of experiments

These types of experiments cannot be initiated without submission of relevant information on the proposed experiments to the Office of Biological Activities (OBA), publication of the proposal in the Federal Register for 15 days of comment, review by the Recombinant DNA Advisory Committee (RAC), and specific approval by the National Institutes of Health (NIH). This type of experiment would be the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally if such acquisition could compromise the ability to control disease agents.

III B: Require OBA approval and IBC approval prior to initiation of experiments

These types of experiments require containment conditions that will be determined by OBA. Types of experiments would include those that have a deliberate formation of r/s NA molecules containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD₅₀ of ≤ 100 ng/kg.

III C: Requires IRB, IBC, and RAC review before participant enrollment

Any experiment involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human research subjects would fall into this category.

III D: Requires IBC approval before initiation of experiments

This group would include using Risk Group (RG) 2,3,4, or restricted agents as Host-Vector systems; experiments in which recombinant or synthetic nucleic acid molecules from RG2, RG3, RG4, or restricted agents is cloned into nonpathogenic prokaryotic or lower eukaryotic Host-Vector systems; experiments involving the use of infectious DNA or RNA viruses or defective DNA or RNA viruses in the presence of helper virus in a tissue culture system; experiments involving whole animals and plants requiring RG2 or higher containment; and experiments involving >10 liters of culture.

III E: Requires IBC notification simultaneous with initiation of experiments

This group would include experiments involving the formation of r/s NA molecules containing no more than ⅓ of the genome of any eukaryotic virus; experiments involving rDNA-modified whole plants, and the generation of transgenic rodents- including the crossing of 2 previously-generated transgenic rodents.

III F: Exempt from NIH Guidelines

This group would include experiments in which the recombinant or synthetic nucleic acid molecules is not in an organism or virus; those that consist entirely of DNA segments from a single non-chromosomal or viral DNA source though one or more of the segments may be a synthetic equivalent; those that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host or when transferred to another host by well-established physiological means, those that consist entirely of DNA from a eukaryotic host when propagated only in that host; those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes though one or more of the segments may be a synthetic equivalent, and those that do not present a significant risk to health or the environment as determined by the NIH Director and the RAC.

Responsibilities when using r/s NA Molecules

The safe conduct of experiments involving recombinant or synthetic nucleic acid molecules depends on the individual conducting these activities. Motivation and good judgment are the key essentials to protection of health and the environment. The [NIH Guidelines](#) are intended to assist the institution, the Institutional Biosafety Committee, the Biological Safety Office, and the Principal Investigator in determining safeguards that should be implemented.

It is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines, as well as to the specifics of the NIH Guidelines. Each institution is responsible for ensuring that all research with recombinant or synthetic nucleic acid molecules conducted at, or sponsored by, the institution is conducted in compliance with the NIH Guidelines. The following responsibilities constitute an administrative framework in which safety is an essential and integral part of the research and acceptable to NIH.

Institutional Responsibilities

1. Establish and implement policies that provide for the safe conduct of r/s NA molecules research and ensure compliance with the NIH Guidelines.
2. Establish an Institutional Biosafety Committee (IBC).
3. Establish a biosafety officer (BSO) if the institution either conducts r/s NA molecules research at BSL-3 or BSL-4; and/or engages in large scale (>10 liters) research.
4. Appoint at least one individual with expertise in plant, plant pathogen, or plant pest containment principles if it conducts r/s NA molecules research in plants.
5. Appoint at least one individual with expertise in animal containment principles if it conducts r/s NA molecules research in animals.
6. Ensure that when the institution participates in or sponsors r/s NA molecules research involving human subjects, it complies with all NIH Guidelines regarding human subject protection.
7. Assist and ensure compliance with NIH Guidelines by PIs conducting the research.
8. Ensure appropriate training for IBC members, PIs, and laboratory staff regarding laboratory safety and the implementation of the NIH Guidelines.
9. Determine the necessity for health surveillance of personnel working with r/s NA molecules.
10. Report any significant problem, violations of the NIH Guidelines, or significant research-related accidents to OBA.

IBC Responsibilities

1. Reviewing r/s NA molecules research for compliance with the NIH Guidelines.
2. Notifying the PI of results of IBC review.
3. Lowering containment levels for certain experiments as detailed in the NIH Guidelines.
4. Setting containment levels as specified by the NIH Guidelines.
5. Periodically reviewing r/s NA molecules research at the institution to ensure compliance.
6. Adopting emergency plans covering accidental spills and personnel contamination resulting from r/s NA molecules work.
7. Reporting any significant problem, violations of the NIH Guidelines, or significant research-related accidents to OBA.
8. Not authorizing the initiation of experiments that are not explicitly covered by the NIH Guidelines until the NIH establishes the containment requirements.

BSO Responsibilities

1. Periodic inspections to ensure laboratory standards are rigorously followed.
2. Reporting to the IBC any significant problem, violations of the NIH Guidelines, or significant research-related accidents.
3. Developing emergency plans covering accidental spills and personnel contamination resulting from r/s NA work.
4. Providing advice on laboratory security.
5. Providing technical advice to PI and IBC on research safety procedures.

PI Responsibilities

1. Do not initiate or modify any r/s NA molecules research that requires IBC approval prior to the initiation of such research until approval is received. This would include exempt r/s NA molecules research at UConn Health.
2. Report to the IBC any significant problem, violations of the NIH Guidelines, or significant research-related accidents to the BSO.
3. Report any new information bearing on the NIH Guidelines to the IBC.
4. Be adequately trained in good microbiological techniques.
5. Adhere to IBC emergency procedures.
6. Comply with shipping requirements for r/s NA molecules.

Recombinant DNA Advisory Committee (RAC)

The RAC is a committee that is responsible for carrying out functions specified in the [NIH Guidelines](#). It consists of no less than 15 voting members appointed under the procedures of the NIH and DHHS. A majority of the voting members must be knowledgeable in relevant fields (microbiology, molecular medicine, etc.) and at least four members must be knowledgeable in fields such as public health, lab safety, ethics, or law. This committee has numerous responsibilities, including:

1. Advise the NIH Director on adopting changes to the [NIH Guidelines](#), assign containment levels, promulgate and amend list of classes of r/s NA molecules to be exempt from the [NIH Guidelines](#), and certify new Host-Vector systems.
2. Identify novel human gene transfer experiments deserving of public discussion by the full RAC.
3. Transmit to NIH Director specific comments/recommendations about specific human gene transfer experiments or categories of human gene transfer experiments.
4. Public review of human gene transfer clinical trial data and relevant information evaluated and summarized by NIH/OBA.
5. Identify broad scientific, safety, social, and ethical issues relevant to gene therapy research.
6. Identify moral, social, and ethical issues relevant to specific human applications of gene transfer.

Office of Biological Activities (OBA)

OBA is the Office in the NIH that has oversight for all research utilizing recombinant and synthetic nucleic acid molecules. It has numerous responsibilities, including:

1. Monitor scientific progress in human genetics research in order to anticipate future developments in basic and clinical research involving r/s NA molecules.
2. Manage the operation of, and provide analytical support to, the RAC, DHHS Secretary's Advisory Committee on Genetics, Health, and Society and the DHHS Secretary's Advisory Committee on Xenotransplantation.
3. Coordinate with the federal and non-federal national and international organizations concerned with r/s NA molecules.
4. Provide advice to the NIH Director, other federal agencies, and state regulatory organizations concerning r/s NA molecules research.
5. Respond to requests for information on highly technical matters and matters of public policy related to r/s NA molecules, human gene transfer, genetic technologies, and xenotransplantation.
6. Develop and implement NIH policies and procedures for the safe conduct of r/s NA molecules activities and human gene transfer.
7. Develop registries of activities related to r/s NA molecules research and human gene transfer.
8. Review and approve experiments involving the cloning of genes encoding for toxin molecules that are lethal for vertebrates at an LD50 of ≤ 100 ng/kg.

Frequently Asked Questions

All I am doing is importing already-made transgenic animals. Why am I asked to provide information about them?

Imports of transgenic animals (from institutional or commercial vendors) are generally exempt from [NIH Guidelines](#) but only if they can be contained at ABSL-1. Any purchase or transfer of transgenic animals that require ABSL-2 conditions (or higher) must be registered with the IBC. In addition, the UCH IBC requires, as an IBC policy, that all genetically manipulated animals that are being imported from a non-domestic source require registration with the UCH IBC. We ask for information about how animals are made to ensure compliance with [NIH Guidelines](#) given that most animals are going to be used for breeding. See the next question.

I have two transgenic rodents that I want to breed. What category does this fall into?

The creation of a new transgenic rodent by breeding two strains that can be housed under ABSL-1 conditions are covered under section III E of the [NIH Guidelines](#). Breeding of transgenic animals is considered an exempt experiment under the [NIH Guidelines](#) with two exceptions: (1) neither parental transgenic rodent contains the following genetic modifications: (i) incorporation of more than one-half of the genome of an exogenous eukaryotic virus from a single family of viruses; or (ii) incorporation of a transgene that is under the control of a gamma-retroviral long terminal repeat (TLR) and (2) the transgenic rodent that results from this breeding is not expected to contain more than one-half of an exogenous viral genome from a single family of viruses. This is

why we ask for information on imports as to how your transgenic lines was made. We need to be sure that the breeding of any animal is compliant with the NIH Guidelines. The creation of a new transgenic rodent by breeding two strains that require BL-2, BL-3, or BL-4 containment are covered under Section III D of the NIH Guidelines and require IBC approval prior to initiation.

I am performing an experiment where cells previously transfected with rDNA are being adoptively transferred into rodents. What category does this fall into?

This type of experiment is covered under Section III D of the NIH Guidelines and requires IBC approval prior to initiation.

I am performing an experiment in which established mouse lymphoma cells carrying an expression plasmid expressing chicken ovalbumin are injected into mice. What category does this fall into?

This type of experiment is covered under Section III D of the NIH Guidelines and requires IBC approval prior to initiation.

I am performing an experiment in which cells are harvested from a transgenic rodent and transferred into an unlike rodent strain. What category does this fall into?

This type of experiment is covered under Section III D of the NIH Guidelines and requires IBC approval prior to initiation.

I am performing an experiment where I will perform a parabiosis between different transgenic strains of mice and transgenic strains with wildtype mice. What category does this fall into?

This type of experiment is covered under Section III D of the NIH Guidelines and requires IBC approval prior to initiation.

Upcoming Training, July 2016 – September 2016

New Animal Users Initial Basic Core Training Monday, September 12
Low Learning Center

9:00 am – 12:30 pm

PLEASE NOTE: Individuals who wish to attend training must complete a registration form and submit it to the IACUC office. Forms and instructions are located on the web at <http://iacuc.uchc.edu/training/initialtraining.html>.

PLEASE NOTE: All individuals working at the UCH starting 9/1/13 or later must complete animal training documentation. The document can be found on the web at http://iacuc.uchc.edu/documents/protocols/training_records_form.docx. We will be copying this information, or asking that they be sent to the IACUC office, when we perform semi-annual inspections in June and December.

New Institutional, State, or Federal Regulations

Institutional

None

State

None

Federal

New MOU between OLAW, USDA, and FDA. If you'd like to see it, you can find it on the web at <http://grants.nih.gov/grants/olaw/references/finalmou.htm>

Important Reminders to Principal Investigators

⚙️ When an individual leaves your laboratory, and is no longer an active animal user, you **must** contact the IACUC Office (ooacc@uchc.edu) with this information.

⚙️ Always remember to list **ALL** transgenic animals and their origin when filling out the Animal Care and Use application in the Recombinant DNA section.

⚙️ Be up-to-date with IACUC Policies. They are all on the web at <http://research.uchc.edu/animal/iacuc/policies/>.



Next Issue: Alternatives Search

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