NIH Guidelines for rDNA Research:

Tutorial for Completing Penn’s rDNA Registration Document
REGISTRATION DOCUMENT FOR RECOMBINANT DNA RESEARCH

Principal Investigator: _____ PennID: _____ Position Title: _____
School: _____ Department: _____
Mailing Address: _____ Mail Code: _____
Telephone: _____ FAX: _____ E-mail: _____
Date of Request: _____ Location of Lab(s): _____

PROJECT INFORMATION
A. Project Title: _____
B. Names of individuals participating in this project:

<table>
<thead>
<tr>
<th>Name</th>
<th>Penn ID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. Provide a brief description of proposed research: _____
D. Attach copy of grant abstract.
E. DUAL USE RESEARCH
   Check any categories below that apply to your project:
   - Renders a useful vaccine ineffective
   - Increases antibiotic resistance affecting response to a clinically useful drug
   - Enhances pathogen virulence
   - Widens a pathogen’s host range
   - Lets a pathogen evade diagnostic or detection modalities
   - Weaponization (e.g., environmental stabilization of pathogens)
   - Check here if none of the above apply

TRAINING
A. Have you read the most current NIH guidelines for research involving rDNA? [No] [Yes]
B. Have the PI and ALL personnel participating in this research completed Penn’s Online Recombinant DNA Training? [No] [Yes]
C. Are you knowledgeable about the appropriate Biosafety Level for this project? [No] [Yes]

NIH GUIDELINES “SECTION III”
This section describes experiments covered by the NIH Guidelines. Check the appropriate registration category(s) for your experiment:
(Note: No research may be initiated for categories A through D below until ALL required approvals are received.)

U.A. Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation:
   1. Major Actions (see Section V.C.1.c.1) of the NIH guidelines.
   1a. Deliberate transfer of drug resistance traits to microorganisms that are unknown to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine or agriculture.

U.B. Experiments that Require HHSOBRA and institutional Biosafety Committee Approval Before Initiation:
   1. Experiments Involving the Cloning of Toxin Molecules with LD50 of Less than 100 Nanograms/kg Kilogram Body Weight.

U.C. Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approval and NIH Guidelines Approval Before Initiation:
   1. Experiments Involving the Deliberate Transfer of Recombinant DNA or RNA Derived from Recombinant DNA into One or More Human Subjects (human gene transfer).

U.D. Experiments that Require Institutional Biosafety Committee Approval Before Initiation:
   2. Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is inserted into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems.
   3. Experiments Involving the Use of Infectious DNA or RNA Virus or Defective DNA or RNA Virus in the Presence of Helper Virus in Tissue Culture Systems.
   4. Experiments Involving Whole Animals. (Do not check if only generating transgenic rodents [fill in 1G].)
   5. Experiments Involving Whole Plants.
   7. Experiments Involving Influenza Viruses (Consult with EHS for guidance. RAC approval may apply.)

U.E. Experiments that Require Institutional Biosafety Committee Approval with Initiation:
   2. Experiments Involving Whole Plants.
   3. Experiments Involving Transgenic Rodents

This registration is for (check the one section that applies):
[ ] CROSSING two different transgenic rodents requiring BSL-2 or higher containment  Fill out Section “1”, ONLY
[ ] CREATING transgenic rodents  Fill out Section “2”, ONLY
[ ] GENERATION of rDNA  Fill out Section “3”, ONLY
[ ] USE of rDNA (including rDNA received from Vector Core, gifted, etc.)  Fill out Section “4”, ONLY
[ ] Both GENERATION and USE of rDNA  Fill out Section “5”, ONLY

FORM MODIFIED 03.08.2011
Definition: “Research that yields information or technologies with the potential to be misused to threaten public health or other aspects of national security.”

Identify this on Penn’s rDNA registration form:

- Dual Use Research Check any categories below that apply to your project:
  - Renders a useful vaccine ineffective
  - Adds antibiotic resistance affecting response to a clinically useful drug
  - Enhances pathogen virulence
  - Increases pathogen transmissibility
  - Widens a pathogen’s host range
  - Lets a pathogen evade diagnostic or detection modalities
  - Weaponization (e.g., environmental stabilization of pathogens)
  - Check here if none of the above apply

- Training
  - Have you read the most current NIH guidelines for research involving rDNA? □ No □ Yes
  - Have the PI and ALL personnel participating in this research completed Penn’s Online Recombinant DNA Training? □ No □ Yes
  - Are you knowledgeable about the appropriate Biosafety Level for this project? □ No □ Yes
Training Requirements

- All personnel who are listed on a registration document must complete training, including:
  - PI
  - Anyone directly involved in rDNA experiments

- Registrations will not be approved until all training is complete

- Training module can be found on Knowledge Link
Know the NIH Guidelines “Section III”

NIH GUIDELINES “SECTION III”

This section describes experiments covered by the NIH Guidelines. Check the appropriate registration category for your experiment:
(Note: No research may be initiated for categories A through D below until all required approvals are received.)

III-A. Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation.
- 1. Major Actions (see Section IV-C.1-b(1) of the NIH guidelines).
- 2. Deliberate transfer of drug resistance trait to microorganisms that are unknown to acquire the trait naturally, if such acquisition could compromise use of the drug to control disease agents in humans, veterinary medicine or agriculture.

III-B. Experiments that Require NIH OBA and Institutional Biosafety Committee Approval Before Initiation.
- 1. Experiments Involving the Cloning of Toxin Molecules with LD50 of Less than 100 Nanograms Per Kilogram Body Weight.

III-C. Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/OBA Registration Before Initiation.
- 1. Experiments Involving the Deliberate Transfer of Recombinant DNA or DNA Derived from Recombinant DNA into One or More Human Subjects (human gene transfer).

III-D. Experiments that Require Institutional Biosafety Committee Approval Before Initiation.
- 2. Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Converted into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems.
- 3. Experiments Involving the Use of Infectious DNA or RNA Viruses or Defective DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems.
- 4. Experiments Involving Whole Animals. (Do NOT check if ONLY generating transgenic rodents [III-E-3].)
- 5. Experiments Involving Whole Plants.
- 7. Experiments Involving Influenza Viruses. (Consult with EHS for guidance. BSL-3 containment may apply.)

III-E. Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation.
- 1. Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus.
- 2. Experiments Involving Whole Plants.
- 3. Experiments Involving Transgenic Rodents

- **It is the PI’s responsibility** to know which section of the NIH Guidelines covers his or her rDNA work.

- **Penn’s registration form asks** you to properly identify this information.

- **The following slides will help** you determine appropriate categories.
Know the **NIH Guidelines**

“**Section III**”

**NIH Guidelines “Sections III-A, III-B, III-C”**

- rDNA work requiring **NIH/OBA and IBC approval** before initiation

**NIH Guidelines “Section III-D”**

- rDNA work that must be **approved by the IBC** before initiation

**NIH Guidelines “Section III-E”**

- rDNA work that requires **notification to the IBC** simultaneous to initiation
Examples of work under “Sections III-A, III-B, and III-C”

III-A. Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation.
   □1. Major Actions (see Section IV-C-1-b-(1) of the NIH guidelines).
   □1a. Deliberate transfer of drug resistance trait to microorganisms that are unknown to acquire the trait naturally, if such acquisition could compromise use of the drug to control disease agents in humans, veterinary medicine or agriculture.

III-B. Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval Before Initiation.
   □1. Experiments Involving the Cloning of Toxin Molecules with LD50 of Less than 100 Nanograms Per Kilogram Body Weight.

III-C. Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/OBA Registration Before Initiation
   □1. Experiments Involving the Deliberate Transfer of Recombinant DNA or DNA or RNA Derived from Recombinant DNA into One or More Human Subjects (human gene transfer).

Examples include but are not limited to:

- III-A-1: Major actions requiring IBC, RAC, and NIH Director approval

- III-A-1a: The deliberate transfer of drug resistance to microorganisms not naturally acquiring that resistance
  • If the resistance trait can could compromise the use of a clinically significant drug

- III-B-1: Formation of rDNA containing genes for toxin molecules that are lethal to vertebrates
  • Toxins that have an LD50 of less than 100ng/kg body weight
  • Ex) Botulinum toxins, tetanus toxins, diphtheria toxin, Shigella dysenteriae neurotoxin

- III-C-1: Experiments involving the deliberate transfer of rDNA into human research participants (human gene transfer)
Examples of work under “Section III-D”

Examples include but are not limited to:

- III-D-1: Using lentiviral or adenoviral vectors
- III-D-2: Gene inserts used are from pathogenic microorganisms
- III-D-3: Helper virus is used in tissue culture to enhance pathogenicity of viral vectors
- **III-D-4: ANY rDNA materials that are going into animals**
  - DOES NOT include making transgenic rodents
  - One of the most common categories of work at Penn
- III-D-5: Genetically engineering plants using rDNA and/or using these plants in experiments
- III-D-6: rDNA experiments using >10L of culture
- III-D-7: rDNA work with all influenza viruses with special consideration of:
  - human H2N2 (1957-1968)
  - fully reconstructed 1918-1919 H1N1
  - Highly Pathogenic Avian Influenza (HPAI) H5N1 (Goose/Guangdong/96-like lineage)
Examples of work under “Section III-E”

III-E. Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation.


☐ 2. Experiments Involving Whole Plants

☐ 3. Experiments Involving Transgenic Rodents

Examples include but are not limited to:

– III-E-1: Recombinant eukaryotic virus containing < 2/3 of its genome is propagated in tissue culture

– III-E-2: rDNA plant experiments requiring BSL-1 containment

– III-E-3: Experiments with transgenic rodents requiring BSL-1 containment
  • Creating a transgenic mouse (BSL-1 containment)
  • One of the most common categories of work at Penn

*If BSL-2/ABSL-2 containment is required, it cannot be “Section III-E”*
NEW Exemption:
Change to Section III-E-3 Requirements
(as of January 19, 2011)

Old Requirement:

– Breeding of one or more transgenic rodents to create new transgenic rodents using BSL-1 conditions

– Fell under section III-E-3

– Previously required registration
NEW Exemption: Change to Section III-E-3 Requirements
(as of January 19, 2011)

New Requirement:

- Breeding of almost* all transgenic rodents that require BSL-1 housing is exempt
- Exempt under section III-F-6
- No registration document required

*Exceptions*

The following must be registered:

- Rodents that contain a transgene encoding >50% of an exogenous eukaryotic virus
- Transgenic rodents in which the transgene is under control of a gammaretroviral promotor
- Any breeding experiments that require BSL-2 conditions
Choose the Type of Project

• For each “type” of work, you must submit a separate registration
  – Ex) If you are both making a transgenic animal and using a lentiviral vector, you must submit two separate registrations

• Complete ONLY the section corresponding to your work
  – You should never have two sections completed

• Separate registration forms are required for different vector systems
  – Ex) If you are using both adenoviral and lentiviral vectors, you must submit two registrations
Crossing Different Transgenic Rodents, Section 1
• Complete this section if you are breeding two different transgenic rodent strains to generate a new transgenic strain, where either the parent strains or offspring require BSL-2 or higher containment, contain a transgene encoding more than 50% of an exogenous eukaryotic virus, or contain a transgene under the control of a gamma retroviral virus.
  • Ex) Example: Breeding of knockouts from two different transgenic strains under the conditions mentioned above.

Creating Transgenic Rodents, Section 2
  – Complete this section if you are using rDNA ONLY to create transgenic rodents. (DO NOT fill out any “generation” or “use” sections).
    • Ex) Creating any transgenic rodent.

Generation of rDNA, Section 3
  – Complete this section if you are generating rDNA materials in your laboratory, but are NOT using them.
    • Ex) You generate an rDNA vector for a collaborating researcher.

Use of rDNA, Section 4
  – Complete this section if you are using rDNA materials in your laboratory. This includes all rDNA constructs that you have received from another source.
    • Ex) The Vector Core or collaborator from another institution makes an rDNA construct for your lab and you will be using it in tissue culture, animals, etc.

Both Generation and Use of rDNA, Section 5
  – Complete this section if you are both generating and using rDNA in your laboratory.
    • Ex) You generate an rDNA construct and use it in tissue culture, animals, etc.
Exempt rDNA Experiments

• NIH Guidelines “Section III-F” covers exempt experiments
  – Registration with the IBC is not required

• Exempt experiments are those involving rDNA molecules that:
  – III-F-1: are not in organisms or viruses
  – III-F-2: consist entirely of DNA from single nonchromosomal or viral DNA source
  – III-F-3: consist entirely of DNA from a prokaryotic host when propagated only in that host
  – III-F-4: consist entirely of DNA from an eukaryotic host when propagated only in that host (excluding DNA from viruses)
  – III-F-5: consist entirely of DNA from different species that exchange DNA by known physiological processes (list periodically updated in Appendices A-I through A-VI)
  – III-F-6: do not present significant risk to health or to the environment as determined by NIH Director with the advice of RAC
Penn’s rDNA Registration Review Process

• Submit the completed and signed registration forms to EHRS
  – E-mail: approvals@lists.upenn.edu
  – Fax: 215-898-0140

• A biosafety officer will review it and contact you with any questions or necessary revisions

• The Institutional Biosafety Committee (IBC) reviews registrations once a month
  – The IBC is not permitted to review registrations outside of a fully convened meeting
  – SO
  – Please be sure to submit registrations in a timely fashion
  – See EHRS website for Penn’s IBC meeting dates
Penn’s rDNA Registration Review Process

• If the IBC approves your registration, you will receive an approval letter with:
  – **IBC registration number** (ex. #10-805)
  – The **biosafety level (BSL)** required
  – The **animal biosafety level (ABSL)** required

• Registrations must be renewed every 3 years

• **If your registration is for work requiring IBC approval BEFORE initiation (Sections III-A, III-B, III-C, III-D), you may not start work until an official approval letter has been received**
Additional Resources to Foster NIH Guideline Understanding

• Office of Biotechnology Activities website

• Office of Environmental Health and Radiation Safety’s (EHRS) website for Biological Safety

• Contact a biosafety officer at EHRS
  – Phone: 215-898-4453
  – E-mail: ehrs@ehrs.upenn.edu