Institutional Biosafety Committees
Purpose & Objectives: Training

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“A safe, healthful, and secure environment for scholarship and research.”
Purpose

Design and present training for the George Washington University Institutional Biosafety Committee (IBC) members that meets the requirements of the NIH Guidelines and prepares them for expanded efforts in the review of Recombinant DNA (rDNA) applications.
Biosafety Program Elements

- Organization
- Biosafety Manual (general and lab-specific)
- Registration and Inventory Control
- Risk Assessment and Control of Biohazards
- Biosafety/IBC Committee
- Biosafety Training
- Emergency Response
- Medical Surveillance
- Auditing / Inspection Program
- Documentation & Record Keeping
External Oversight on Biosafety

- National Institutes of Health (NIH)
  - Office of Biotechnology Activities
- Centers for Disease Control (CDC)
- Occupational Safety & Health Administration (OSHA)
- Environmental Protection Agency (EPA)
- US Dept of Agriculture (USDA)
- US Dept of Justice
- US Dept of Transportation
- US Dept of Commerce
- World Health Organization (WHO)
- Community Activist Groups
Internal Oversight on Biosafety

- Institutional Biosafety Committee (IBC)
- Biosecurity and Biosafety Programs
- Emergency Response Plan
- Standard Operating Procedures (SOP’s)
- Laboratory Inspections (internal and external; CDC, USDA, AAALAC, etc.)
- Training and Documentation
- Institutional Animal Care and Use Committee (IACUC)
- Institutional Review Board (IRB)
Institutional Biosafety Committees

- Established under the *NIH Guidelines* specifically for the review of research involving recombinant or synthetic nucleic acid molecules
- IBCs are typically assigned additional review responsibilities
  - Select agents and toxins
  - Blood borne pathogens
  - Xenotransplantation
  - Stem cell research
  - “Dual Use” research
  - Nanotechnology
- Broader purview is a matter of institutional discretion
Institutional Biosafety Committees
Assembling an IBC

◆ Membership
  ◆ At least five individuals
  ◆ Appropriate recombinant and synthetic nucleic acid expertise collectively
  ◆ Plant and animal experts, biosafety officer as appropriate
  ◆ At least two members not affiliated with the institution

◆ Expertise
  ◆ Expertise in assessment of risk to environment and public health
  ◆ Knowledge of institutional commitments and policies, applicable law, professional standards, community attitudes, and environment
  ◆ Biological safety and physical containment
  ◆ Laboratory technical staff (recommended)
Institutional Biosafety Committees
Assembling an IBC

The BSO’s duties include:

- Periodic inspection of labs
- Reporting to the IBC and institution of any problems, violations, research-related accidents or illnesses
- Developing emergency plans for handling accidental spills and personnel contamination
- Advice on lab security
- Technical advice to PIs and the IBC on research safety procedures
Non-institutional members - Who are they?

- Representatives of community interests with respect to health and protection of the environment

- E.g., officials of state or local public health or environmental authorities, local government bodies, persons with medical, occupational, or environmental expertise

- They should be individuals who “represent community attitudes”
In a nutshell, what must IBCs review?

- Research involving recombinant or synthetic nucleic acid molecules for conformity with the NIH Guidelines
- Potential risk to environment and public health
  - Containment levels per NIH Guidelines
  - Adequacy of facilities, SOPs, PI and lab personnel training
  - Institutional and investigator compliance; e.g., adverse event reports
IBC Responsibilities

In basic and preclinical research, IBCs have authority to:

- Lower containment levels for certain experiments in which nucleic acid from Risk Group 2-4 is cloned in non-pathogenic organisms
- Set containment levels for experiments involving whole plants and animals
- Review periodically institutional compliance with NIH Guidelines
- Adopt emergency plans covering spills, contamination, other accidents
For human gene transfer research, IBCs must also ensure:

- No participant enrolled in a trial until RAC review, IBC and IRB approval has been obtained
- Issues raised by the RAC in public review are considered
- Final IBC approval occurs only after RAC review
- PI compliance with surveillance, data reporting, and adverse event reporting
IBCs and Exempt Research

- Should IBCs determine what research is exempt? Should the PI?
  - A matter of institutional policy
  - IBC may wish to designate the chair, a member, or the BSO to conduct an initial review to confirm what is exempt and what requires full IBC review
  - NIH OBA can help with determinations
IBC Coordination with Other Institutional Oversight Committees

- Not prescribed in the *NIH Guidelines*
- Institutions should determine the best way for these committees to interact and share information
Institutional Committees-overlap!

- Relationship not prescribed in the *NIH Guidelines*
- Institutions should determine best way for these committees to interact and share information
Joint purview, and ideally collaborative review, over certain types of research

- Transgenic or cloned animals
- Use of recombinant or synthetic nucleic acid molecules in animals
- Pre-clinical studies and data assessment for human gene transfer protocols
**IBC and IACUC Review of Animal Research Subject to the NIH Guidelines**

<table>
<thead>
<tr>
<th>IBC Review</th>
<th>IACUC Review</th>
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<tbody>
<tr>
<td><strong>Risks to human health</strong></td>
<td><strong>Animal welfare</strong></td>
</tr>
<tr>
<td>- Transfer of genetically altered material, viral vectors etc.</td>
<td>- Pain and distress from adverse phenotypes (behavioral, anatomical and physiological abnormalities)</td>
</tr>
<tr>
<td><strong>Risks to the environment</strong></td>
<td>- Risks to other animals in the facility from the inadvertent spread of vectors</td>
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<tr>
<td>- Escape and establishment in the wild</td>
<td></td>
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<tr>
<td>- Interbreeding with wild stock</td>
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<tr>
<td>- Consumption by other animals</td>
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### IBCs and IRBs – Oversight of Human Gene Transfer Research

<table>
<thead>
<tr>
<th>IRB Review</th>
<th>IBC Review</th>
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<tbody>
<tr>
<td>- Conducts risk/benefit assessment relative to individual research participants (physical, psychological, social harms)</td>
<td>- Research for conformity with the <em>NIH Guidelines</em></td>
</tr>
<tr>
<td>- Selection of subjects and the informed consent process</td>
<td>- Potential risk to environment and public health (risks to close contacts, health care workers, and the community, as well as to individual research participants)</td>
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<tr>
<td>- Data monitoring provisions to ensure the safety of subjects</td>
<td>- Containment levels per <em>NIH Guidelines</em></td>
</tr>
<tr>
<td>- Provisions to protect subject privacy and confidentiality of data</td>
<td>- Adequacy of facilities, SOPs, PI and other personnel training</td>
</tr>
<tr>
<td>- Injuries or any other unanticipated problems</td>
<td>- Institutional and investigator compliance (e.g., adverse event reports)</td>
</tr>
<tr>
<td>- Compliance with regulations</td>
<td>- Reviews trial design, biosafety and containment, and compliance with <em>NIH Guidelines</em></td>
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IBCs and NIH OBA

- NIH OBA provides oversight, guidance, and resources for IBCs
  - Staff and information resources available to help ensure IBCs, their institutions, and investigators are compliant with the *NIH Guidelines*
  - Scientific and medical staff available to answer queries
    - Interpretation of *NIH Guidelines*
    - Containment
    - Exemptions
    - Risk group classification
General Definition related to IBC
Biohazard:
An agent of biological origin that has the capacity to produce harmful effects on humans; i.e. microorganisms, toxins and allergens derived from those organisms, and allergens and toxins derived from plants or animals.

Biosafety:
Applying a combination of laboratory practices and procedures, laboratory facilities, and safety equipment when working with potentially infectious microorganisms.
Risk Assessment: Addressing laboratory activities involving infectious or potentially infectious material and implementing measures to reduce the worker’s and environment’s risk of exposure to an agent to an absolute minimum.
Biosecurity: Protection of high-consequence microbial agents and toxins, or critical relevant information, against theft or diversion by those who intend to pursue intentional misuse.
Biosecurity vs. Biosafety

- **Biosecurity** refers to ensuring the **security** of biological materials to prevent theft, illicit use, or release.

- **Biosafety** focuses on **reducing exposure** to and **release** of biological materials.

- Both involve conducting a **risk assessment** to mitigate risks.
Select Agents:

Pathogens and toxins considered to have the potential to pose a severe threat to human, animal, or plant health and safety.

Viruses
Bacteria
Fungi
Toxins
Responsibilities Under the NIH Guidelines for Research Involving Recombinant DNA Molecules
Recombinant DNA Molecules

• Under the current NIH Guidelines, these are molecules constructed outside of living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or molecules that result from their replication.

NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

A document created in 1976 that outlines principles for the safe conduct of research employing recombinant DNA technology. The NIH Guidelines detail practices and procedures for the containment of various forms of recombinant DNA research, for the proper conduct of research involving genetically modified plants and animals, and for the safe conduct of human gene transfer research.
Who must comply with the NIH Guidelines?

- All institutions that receive National Institutes of Health (NIH) funding for recombinant DNA research must comply with the NIH Guidelines.

- Researchers at institutions that are subject to the NIH Guidelines must comply with the requirements even if their individual projects are not funded by NIH.

- Even though they are called “guidelines,” the NIH Guidelines are a term and condition of NIH funding for recombinant DNA research.

- If your institution is subject to the NIH Guidelines you must follow the requirements and adhere to the practices outlined in the document.
Non compliance with the Guidelines may result in suspension or termination of NIH funds for recombinant DNA research, or the requirement to have all recombinant DNA projects at the institution receive prior NIH approval.
Section II of the *NIH Guidelines* focuses on safety considerations for research with recombinant and synthetic nucleic acids.
Section II – Risk Groups

• Appendix B of the NIH Guidelines lists biological agents known to infect humans as well as selected animal agents that have the potential to infect humans.

• Biological agents are assigned to one of four risk group based on the potential effect of the agent on a healthy human adult.
## Section II – Risk Groups

<table>
<thead>
<tr>
<th>RG 1</th>
<th>RG 2</th>
<th>RG 3</th>
<th>RG 4</th>
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<tbody>
<tr>
<td>Agents that are not associated with disease in healthy adult humans</td>
<td>Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available</td>
<td>Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available (high individual risk but low community risk)</td>
<td>Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available (high individual risk and high community risk)</td>
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</table>
In proposing research, the PI must make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*.

The PI must also propose appropriate microbiological practices and laboratory techniques to be used for the research.
Physical Containment

- Four biosafety levels are described in Appendix G of the *NIH Guidelines*. These biosafety levels consist of a combination of lab practices and techniques, safety equipment, and lab facilities appropriate for the operations being performed.

- **Appendix P** of the NIH Guidelines specifies physical and biological containment conditions and practices suitable to the greenhouse conduct of experiments involving recombinant DNA-containing plants, plant-associated microorganisms, and small animals.

- **Appendix Q** specifies containment and confinement practices for research involving whole animals, both transgenic animals and experiments involving viable recombinant DNA-modified microorganisms tested on whole animals.

- **Appendix Q** supersedes Appendix G when research animals are of a size or have growth requirements that preclude the use of containment for laboratory animals. The animals covered in Appendix Q include but are not limited to cattle, swine, sheep, goats, horses, and poultry.
Biological containment is the application of highly specific biological barriers. Such barriers limit either the infectivity of a vector for specific hosts, or its dissemination and survival in the environment.

Vectors can be genetically designed to decrease, by many orders of magnitude, the probability of dissemination of recombinant DNA outside the lab.
A requirement of the *NIH Guidelines* is that an IBC must review and approve all research subject to the *NIH Guidelines*.

Principal Investigator (PIs) are responsible for determining if their work is requires IBC review and approval because it falls under Section III-A, III-B, III-C, III-D or III-E of the *NIH Guidelines*.

PIs must submit a research proposal for IBC review and obtain IBC approval if the work is subject to Section III-A, III-B, III-C, III-D or III-E of the NIH Guidelines.

IBC approval must be obtained before initiating research subject to Section III-A, III-B, III-C or III-D of the NIH Guidelines.

PIs must determine the need for IBC review before modifying any recombinant DNA research already approved by the IBC.
## Summary of NIH Guidelines: Levels of Review

<table>
<thead>
<tr>
<th>Section of the NIH Guidelines</th>
<th>Level of review</th>
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<tbody>
<tr>
<td>III-A</td>
<td>IBC, Recombinant DNA Advisory Committee (RAC) review, and NIH Director review and approval</td>
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<tr>
<td>III-B</td>
<td>IBC approval and NIH Office of Biotechnology Activities (OBA) review for containment determinations</td>
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<tr>
<td>III-C</td>
<td>IBC and Institutional Review Board (IRB) approval and RAC review before research participant enrollment</td>
</tr>
<tr>
<td>III-D</td>
<td>IBC approval before initiation</td>
</tr>
<tr>
<td>III-E</td>
<td>IBC notice at initiation</td>
</tr>
<tr>
<td>III-F</td>
<td>Exempt from the <em>NIH Guidelines</em>. IBC registration not required if experiment not covered by Sections III-A, III-B, or III-C</td>
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</tbody>
</table>
Section III-A covers experiments that require IBC approval, RAC review and NIH Director approval before they can begin.

These types of experiments are known as “Major Actions” and involve the deliberate transfer of a drug resistance trait to microorganisms, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture.

For more information on Major Actions see:
http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm#_Toc7261561
Section III-B covers experiments that require NIH/OBA review and IBC approval before initiation.

Experiments involving the cloning of toxin molecules with LD50 of less than 100 nanograms per kilogram body weight.
Section III-C experiments require RAC review, IBC approval and IRB approval before initiation.

Deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into one or more human research participants.
Section III-D covers experiments that require IBC approval before initiation

- Section III-D-1: Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems

- Section III-D-2: Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems

![Cloning into a plasmid diagram]
Section III-D

- Section III-D-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.

- Section III-D-4: Experiments Involving Whole Animals
  Includes experiments in which: The animal’s genome has been altered by stable introduction of rDNA into germline (transgenic animals).

- Section III-D-5: Experiments Involving Whole Plants:
  Includes experiments in which: Plants are genetically engineered by recombinant DNA methods. Plants are used with recombinant DNA-modified insects. Generally BL2-P through BL4-P, depending on risk.
Section III-D

- Section III-D-6: Experiments involving more than 10L of culture: See Appendix K of the NIH Guidelines [http://oba.od.nih.gov/oba/rac/guidelines_02/Appendix_K.htm]
Section III-E

- Section III-E describes a class of experiments which require registration with the IBC at the time of initiation.
- All experiments **not** included in III-A through III-D or III-F fall under III-E.
- The IBC still reviews and approves these experiments but this review does not need to occur **before** the experiment commences.

- **Section III-E-1:** Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus. Such molecules may be propagated and maintained in tissue culture using BL1 containment. For such experiments it must be demonstrated that the cells lack helper virus for the specific Families of the defective viruses being used.

- **Section III-E-2:** Covers experiments involving whole plants, and/or experiments involving recombinant DNA-modified organisms associated with plants, except those that fall under Section III-A, III-B, III-D or III-F.
Section III-E

- **Section III-E-3** covers experiments involving the generation of transgenic rodents

- **Section III-E-2**: Covers experiments involving whole plants, and/or experiments involving recombinant DNA-modified organisms associated with plants, except those that fall under Section III-A, III-B, III-D or III-F.
  - *Rodent’s genome has been altered by stable introduction of recombinant DNA into germline*
  - *BSL1 containment is appropriate*
Section III-F describes experiments that are exempt from the NIH Guidelines. Registration with the IBC is not required (unless required by institutional policy). The following recombinant DNA molecules are exempt from the NIH Guidelines:

- III-F-1 – Those that are not in organisms or viruses.
- III-F-2 – Those that consist entirely of DNA segments from a single nonchromosomal or viral DNA source, though one or more of the segments may be a synthetic equivalent.
- III-F-3 – 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.
- III-F-4 – Those that consist entirely of DNA from a eukaryotic host including its chloroplasts, mitochondria or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species).
- III-F-5 – Those that consist entirely of DNA segments from different species that exchange DNA known physiological processes.
- III-F-6 – Those that do not present a significant risk to health or the environment, as determined by the NIH director, with the advice of the RAC, and following appropriate notice and opportunity for public comment.
Overview of Appendix collections

Appendix C-I: Recombinant DNA in Tissue Culture Recombinant DNA molecules containing less than one-half of any eukaryotic viral genome that are propagated and maintained in cells in tissue culture are exempt.

Appendix C-II: Experiments which use *Escherichia coli* K-12 host-vector systems are exempt from the NIH Guidelines provided that: the *Escherichia coli* host does not contain conjugation proficient plasmids or generalized transducing phages; or lambda or lambdoid or Ff bacteriophages or non-conjugative plasmids.

Appendix C-III: Experiments involving *Saccharomyces cerevisiae* and *Saccharomyces uvarum* host-vector systems are exempt from the NIH Guidelines.

Appendix C-IV: Any asporogenic *Bacillus subtilis* or asporogenic *Bacillus licheniformis* strain which does not revert to a spore-former with a frequency greater than $10^{-7}$ may be used for cloning DNA and is exempt from the NIH Guidelines.

Appendix C-V: Recombinant DNA molecules derived entirely from extrachromosomal elements of the organisms listed, propagated and maintained in organisms listed are exempt from the NIH Guidelines.

Appendix C-VI: The purchase or transfer of rodents for experiments that require BL-1 containment.
IBC Protocol Reviews (aka Risk Assessment)
Individuals with different experience will view risk differently

IBCs rely on multiple perspectives to evaluate risk
Recombinant DNA raises possibility of modifying a host or vector to impart new properties not considered in original risk group classification. Requires an understanding of the host/vector system involved, the expression construct, and the finished product.

- Protection of personnel
- Guidance for containment and work practices
Elements of Risk Assessment

For rDNA materials must consider:

**Transgene**
- Effects of the gene product being produced
- Effect of eliminating a gene product

**Vector/host system**
- Intrinsic characteristics (risk group)
- Replication competence
- Residual viral gene expression

**End product**
- Possible introduction or increase of virulence
Gene Product Effects

Local effects
Protein may have deleterious effects on the cell it is expressed in, but can’t spread
  Ion channels, enzymes

Systemic effects
Secreted protein that can disseminate and exert an effect on otherwise unmodified cells
  Cytokines, growth factors
A protein that modifies a cell so that this cell becomes a threat
  Oncogenes
RNAi used to knock-down expression of a normal cellular protein

Will the effect of this change be:

- Local? (i.e. eliminating an enzyme in a metabolic pathway)
- Disseminated? (i.e. eliminating a protein that regulates growth control)

Off-target effects
Bacterial Vector Considerations

Basic characteristics of organism
  Pathogenicity
  Ability to persist in host

Mobile Genetic Elements
  Plasmids
  Insertion sequences and transposons
  Bacteriophages
  Ability to shuttle virulence factors
Viral Vector Considerations

Pathogenicity of parental virus
Cytopathogenicity of vector
Scale-up considerations
Requirements for specialized facilities
Training requirements
End Product Concerns

Increased risk over vector alone
  Introduction of virulence factors
    Toxins, antibiotic resistance
    Increased ability to evade immune system
  Efficient delivery of a product with disseminated effects

Reconstitution of replication competence

Concern: creation or restoration of pathogenicity
Host/Vector Interactions

Evade/defeat host immune system
  Limited exposure to immune system
  Latency
  Gene products to suppress immune response or interfere with immune recognition

Adherence to host cell
  Surface protein on agent recognizes cell-surface molecule (generally protein)
  Responsible for tropism and host range of agent
Host/Vector Interactions

Penetration
- Cells take up agent (result of binding, phagocytosis)
- Fusion proteins, nuclear localization signals

Colonization and multiplication
- Attachment factors (capsules, pili)
- Virulence factors (toxins, antibiotics)
- Commandeer host cell metabolism

Spread
- Escape from cell, access to circulation
Some rDNA work is reasonable to do at BSL1 level

Things to consider

- Exposure of user to vector system/cDNA
  - Route of infection
  - Effect of gene product
  - Persistence in host

- Environmental release
  - Persistence in the environment
  - Nothing gets out alive!

What is Low Risk?
What Factor Can Escalate Risk?

Cascade of infection
  Evade/defeat host immune system
  Adherence to host cell
  Penetration
  Colonization and multiplication
  Spread

Gene products derived from either host or vector systems that are involved in, or could enhance these processes can be concerns in rDNA work.
Reducing Risk

The usual
  - Containment (engineering controls)
  - Work practices
  - PPE

Lower risk agent
  - Is that vector necessary, or convenient?
  - Latest generation vectors

Can the experiment be changed to be done more safely, yet still answer the question?
What Should IBC member Ask About SOP?

Do you have the information you need?

- Scale of work
- Replication competent virus testing
- Location of work
- Knowledge/training/experience of personnel
- **Details** of vector system (not ‘adenovirus vector’)
- **Details** of the gene product and its action
- **Details** of the work to be done
The Standard Code of Practice for Biosafety

Biosafety in Microbiological and Biomedical Laboratories (BMBL)
U.S. Department of Health & Human Services
Public Health Service
Centers for Disease Control & Prevention & the National Institutes of Health
http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm

Establishes criteria for:

- Biological Risk Assessment
- Principles of BioSafety
- Laboratory BioSafety Level (BSL) Criteria
- Laboratory BioSecurity Criteria
- BioHazard Containment
- Decontamination & Disinfection
- Transportation of BioHazards & Infectious Materials
- Select Agents & Toxins…
Promoting Health Security

- Raising awareness
- Preparedness for intentional release: Pathogen Control

National Biosafety Strategy

- Legislative (Regulations)
- Guidelines
- Education & Training
- Biosafety specialists

Partnering and Cooperation

- Developing risk assessment methodologies
- Capacity-building for risk management

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC
Thank you

Be Safe Not Sorry

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