BIO 100 - Introduction to the NIH Guidelines for Recombinant DNA

Learning Objectives

This course is an introduction to the National Institute of Health (NIH) Guidelines for recombinant DNA (rDNA). In this training, we will:

- Discuss the history of rDNA oversight
- Outline the rDNA program at the Office of Biotechnology Activities (OBA)
- Identify the NIH Guidelines and responsibilities associated with them
- Introduce the Institutional Biosafety Committee (IBC)
- Outline training requirements
- Locate guidance materials and helpful resources

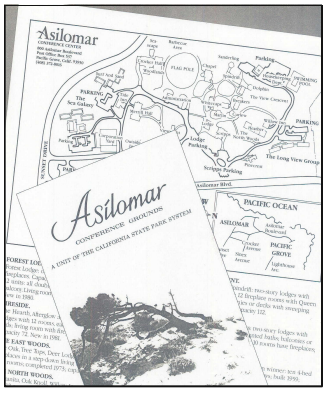
A Brief History of rDNA Oversight

Emergence of rDNA

The emergence of rDNA technology in the mid 1970's led to:

- Concerns among both the scientific community and the general public with regard to:
  - Public health and safety
  - Environmental impact, and
  - Potential ethical and social implications
- As a result, a subsequent National Academy of Sciences (NAS) Committee Report (July 1974) called for:
  - A moratorium on certain experiments, and
  - The development of NIH guidelines for the conduct and review of rDNA experiments

Asilomar Scientific Summit



A big turning point in rDNA work was the Asilomar Scientific Summit (1975) which was organized by a group of scientists with the following results:

- The Premise:
  - Scientists taking responsibility for the risks of their own research activities
- The Outcomes:
  - Reaffirmation of the need for rDNA guidelines
  - The establishment of a new federal oversight committee

The RAC

The NIH Recombinant DNA Molecule Program Advisory Committee (the "RAC")

- Is the first federal advisory committee
- Launched the process of developing NIH guidelines for rDNA oversight
- Made recommendations about local oversight of rDNA

- NIH grants using rDNA can be awarded only after review of risks by an institutional “biohazards” review committee or an IBC (Institutional Biosafety Committee)
  - This includes review of the physical containment and facilities available for the experiments, and
  - Consideration of local circumstances

First NIH Guidelines

The First NIH Guidelines for rDNA

- Were published in July 1976
- These guidelines established responsibilities for both investigators AND institutions
- The Guidelines are a scientifically-responsive document that will continue to evolve
  - They have already undergone multiple revisions since 1976
  - Visit the Office of Biotechnology Activities website for the latest version

Local Community Involvement

- Local communities (e.g., Cambridge, Massachusetts) begin establishing their own oversight frameworks
- Local review and citizen involvement are key characteristics of oversight

Policing genetic research

THE WASHINGTON POST Friday, July 9, 1976

City Blocks DNA Research

By Edward Schumacher
Special to The Washington Post

CAMBRIDGE, Mass., July 8— The Cambridge City Council early this morning voted a three-month moratorium on potentially dangerous genetic research at Harvard University and Massachusetts Institute of Technology that federal research officials fear will set a precedent of community control over such work.

The nine-member council voted 5 to 3 with one abstention to establish a review committee of scientists and citizens to recommend by the end of the moratorium a city policy on the "recombinant DNA" research. The city has the legal power to ban the experiments by declaring them a public health hazard.

Mayor Alfred E. Vellucci, who is also head of the city council, said today, "Cambridge has six square miles and we're boss here. They're going to do what we tell them."

The moratorium will have little effect on the university for the time being. Harvard does not plan to have the requisite laboratory until next spring. MIT has a lab, but it has not been certified yet under new federal guidelines on such research.

ganism. The possibility exists that it will be an unknown one and that its properties will be unpredictable, scientists on all sides of the issue agree.

The fear is that new diseases with unknown cures will be created and spread.

Proponents of the research say that it offers the basic scientific understanding of cell reproduction that could lead to cures for cancer and other diseases, as well as to the production of organic things such as insulin and self-fertilizing plants.

William J. Garland, head of genetic research at the National Institutes of Health, attended the five-hour hearing, which was packed with several hundred local residents, students, scientists and two Nobel laureates. He later said the council's action may be "obstructive" by starting a wave of non-uniform regulations across the country.

He said the recombinant research is expected to escalate rapidly. A voluntary national moratorium on the research had been in effect since 1974 until two weeks ago when NIH issued long-awaited guidelines on the safety issue.

intellectuals opposing the genetic research. These include outspoken Nobel laureate George Wald and his wife, Ruth Hubbard, as well as many of the university students Vellucci has ridiculed in the past.

"It's nice to know the city can expose an issue like this and have all the Nobel scientists come to us" Vellucci said.

Attention has centered on Harvard, where recently the administration approved plans for a recombinant DNA lab in the biology building after months of debate among students and professors. One biology professor opposing the work has since demanded her office be moved farther away from the lab.

Harvard geneticist William Petrie said at the hearings that the lab should be moved to a desert area. "If it blows up, only a few persons will be hurt," he said.

But Matthew S. Meselson, chairman of the department of biochemistry and molecular biology and a supporter of the research, said that if he thought the lab were dangerous, "I would not subject myself to it . . . The work is too important to be

Enhancing Public Access

Enhancing Public Access (new addition to the guidelines in 1978)

- At least two, and no less than twenty percent, of IBC members had to represent the general public and have no connection to the institution
- The “important records” of the IBC’s had to be made publicly available
  - In addition to meeting minutes these include MUAs (Memorandum of Understanding Agreements), reports of violations, and other materials submitted to the federal government
- “Major actions” (such as human gene therapy trials) can only be carried out on the advice of the RAC and after public and Federal agency comments are received
- Public participation continues to be a hallmark of rDNA oversight

Questions and Concerns

- Hasn't history proven the technology to be safe?
- Why do we have a technology-based approach to oversight instead of one that is based on the risks of individual products?

Are there really Any Residual Concerns?

The public here and abroad is still concerned about many aspects of this technology. Our oversight system has provided scientifically-based surveillance of this research that has reassured the public and permitted the science to move forward safely.
Human gene transfer, however, continues to raise many safety, ethical, and scientific issues in need of public discussion and analysis.

The OBA

The rDNA oversight entity - the NIH Office of Biotechnology Activities (OBA):

- Lies administratively within the Office of Science Policy of the Office of the Director of the NIH

- Has five programs which oversee the following:
  - Recombinant DNA (RAC)
  - Genetics (SACGHS – Secretary's Advisory Committee on Genetics, Health and Society; issues regarding genetics and genomics technology and society)
  - Xenotransplantation - the use of live animal cells, tissues and organs in the treatment or mitigation of human disease (SACX)
  - Biosecurity (NSABB)
  - Outreach and Education

rDNA Program at OBA

Recombinant DNA Program at OBA:

- Oversees recombinant DNA research, including human gene transfer
- Manages the Recombinant DNA Advisory Committee (RAC)
- Administers the NIH Guidelines for Research Involving Recombinant DNA Molecules
- Partners with Institutional Biosafety Committees in the oversight of recombinant DNA research
- Disseminates information on technical and policy matters concerning recombinant DNA research, such as:
  - RAC recommendations on clinical protocols
  - Interpretations of the NIH Guidelines
  - Scientific symposia and policy conferences
- Develops and contributes to public policy on recombinant DNA research
  - Interagency oversight of biotechnology

The NIH Guidelines – Section I

Scope

- The Guidelines specify appropriate practices for constructing and handling:
  - Recombinant DNA molecules; and
  - Organisms and viruses containing recombinant DNA molecules

- **Definition of rDNA**:
  - Constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell
  - Molecules resulting from the replication of those described above

NIH Guidelines

The NIH Guidelines Apply to…

Recombinant DNA research that is:

- Funded by the NIH
- Performed at or sponsored by an institution that receives any NIH funding for recombinant DNA research

Rationale: For biosafety to be meaningful, it has to be observed by all investigators at an institution

Are the NIH Guidelines Optional?

- **"Guidelines" does not mean "optional"**
- They are a term and condition of NIH funding for recombinant DNA research
- If ANY NIH grants are received by your Institution, then **all** of the projects involving recombinant DNA at your institution, even those which are privately funded, are then subject to the requirements of the Guidelines.

NIH Guidelines

So what happens if we ignore the Guidelines?

What are potential consequences of noncompliance with the NIH Guidelines? Non compliance with the Guidelines does have potential consequences which could include:

- The suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or

- A requirement for prior NIH approval of any or all recombinant DNA projects at the institution (a time-consuming operation given that the OBA has limited staff available for this task).

NIH Guidelines – Section II

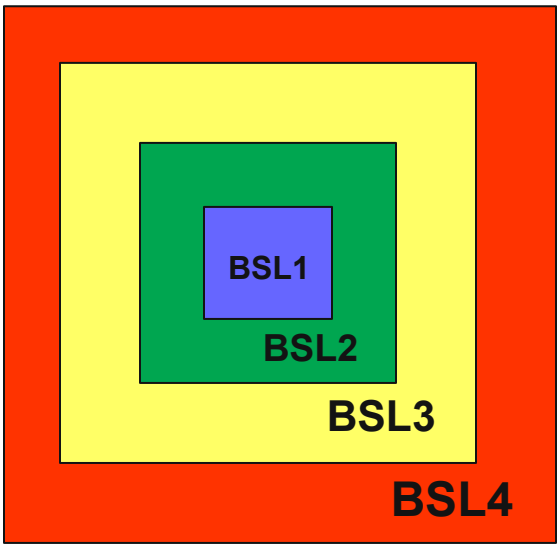
Safety Considerations

- Risk assessments for the organisms and DNA source organisms: agents are classified into four risk groups by the NIH and the CDC based upon the following criteria (Appendix B):

RG1	RG2	RG3	RG4
Agents that are not associated with disease in healthy adult humans	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are **often** available	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)	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)

Containment of DNA and organisms can be either:

- Physical (outlined in Appendix G)
  - Lab Practices
  - Safety Equipment/facilities; or
- Biological (outlined in Appendix I)
  - Survival in the environment
  - Transmission of genetic elements or disease



NIH Guidelines - Section III

Levels of Review

Level of review	Example of recombinant DNA research involving animals	Relevant section(s) of the NIH Guidelines
IBC, RAC review, and NIH Director review and approval	Deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally.	III-A
IBC approval and NIH review for containment determinations	Experiments involving the cloning of toxin molecules with LD50 of less than 100 nanograms per kilogram body weight. Examples: botulinum, tetanus, and diphtheria toxins; S. dysenteriae neurotoxin.	III-B
IBC and IRB approval and NIH review before research participant enrollment	Experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into a human subject.	III-C
IBC approval before initiation	Work in which DNA from risk group 2, 3, 4, or restricted human or animal pathogens is cloned in nonpathogenic prokaryotic or lower eukaryotic host-vector systems. a. cloning of DNA from risk group 2 or 3 agents can be carried out at BL2. b. cloning of DNA from risk group 4 agents can be carried out at BL4 unless a totally and irreversibly defective fraction of the genome was cloned (BL2). c. cloning of DNA from restricted agents is a case-by-case situation. d. specific lowering of containment to BL1 for particular experiments can be approved by IBC. e. some of these experiments may be deemed exempt by the IBC.	III-D
IBC notice at initiation	Experiments involving the formation of recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus.	III-E

Exempt from the NIH Guidelines. IBC registration not required if experiment not covered by Sections III-A, III-B, or III-C	Recombinant DNA molecules that are not in organisms or viruses. Recombinant DNA molecules that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species) or when transferred to another host cell by well established physiological means.	III-F

NIH Guidelines -- Appendix G-II-B-2-k

Incident reporting for BSL2 and higher experiments:

- Spills and accidents which result in overt exposures to organisms containing recombinant DNA molecules are immediately reported to the Institutional Biosafety Committee and NIH/ OBA.

- Reports to NIH/OBA shall be sent to:
  Office of Biotechnology Activities, National Institutes of Health
  6705 Rockledge Drive, Suite 750, MSC 7985
  Bethesda, MD 20892-7985 (20817 for non-USPS mail)
  Phone: (301) 496-9838
  Fax: (301) 496-9839

- Medical evaluation, surveillance, and treatment are provided as appropriate, and written records are maintained.

Responsibilities under the NIH Guidelines

Institutional

Argonne shall:

- Establish and implement policies for the safe conduct of recombinant DNA research
- Establish an Institutional Biosafety Committee
- Assist and ensure compliance with the NIH Guidelines by investigators
- Ensure appropriate training for IBC members and staff, Principal Investigators (PIs), laboratory staff
- Determine necessity for health surveillance of personnel
- Report any significant problems or violations to OBA within 30 days

Principal Investigator

The Principal Investigator (PI) shall (among other things):

- Initiate or modify no recombinant DNA research which requires IBC review until approval is granted
- Determine whether experiments are covered under III-E or F and notify the IBC as appropriate
- Be adequately trained in good microbiological techniques
- Adhere to IBC emergency plans for spills and personnel contamination
- Report any significant problems or violations to OBA within 30 days

NIH OBA

NIH OBA (on behalf of the NIH Director) is responsible for:

- Managing the RAC
- Conducting and supporting training of IBCs, BSOs, investigators, laboratory staff
- Convening Scientific Symposia and Gene Therapy Policy Conferences
- Review of human gene transfer protocols and certain basic recombinant DNA experiments
- "Minor actions" - changes not requiring approval by the NIH Director
- Basic recombinant DNA experiments reviewed by NIH OBA
    - Deliberate transfer of drug resistance trait to microorganisms not known to acquire the trait naturally, if it could compromise disease control
    - Cloning of toxin molecules with LD_{50} <100 ng/Kg bodyweight
    - DNA from restricted agents transferred to nonpathogenic prokaryotes or lower eukaryotes
    - DNA from nonpathogenic prokaryotes or lower eukaryotes transferred to restricted agents
    - Use of infectious or defective restricted poxviruses in presence of helper virus

Good Judgment is Key!

The NIH Guidelines will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, 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.

- **Good judgment is key**
- **OBA can help**

IBCs

Institutional Biosafety Committees:

- Are the key institutional component of a national system of oversight
- Are "sentinels" at the local level, identifying new safety and policy issues for NIH OBA and RAC consideration
- Are established specifically for the review of recombinant DNA research
- Often review other research with biohazardous risks
    - Infectious agents, carcinogens
    - Broader purview is a matter of institutional discretion

Assembling an IBC

Membership

- No fewer than 5 individuals
- Appropriate recombinant DNA expertise collectively
- Plant and animal experts, biosafety officer as appropriate
- Expertise in assessment of risk to environment and public health
- At least two members not affiliated with the institution

Additional expertise

- Biological safety, and physical containment
- Knowledge of institutional commitments and policies, applicable law, professional standards, community attitudes, and environment
- Laboratory technical staff (recommended)

Non-institutional members

- Representatives of community interests with respect to health and protection of the environment
- For example, officials of state or local public health or environmental authorities, local government bodies, persons with medical, occupational, or environmental expertise
- They can also be the individuals who “represent community attitudes”

Registering an IBC

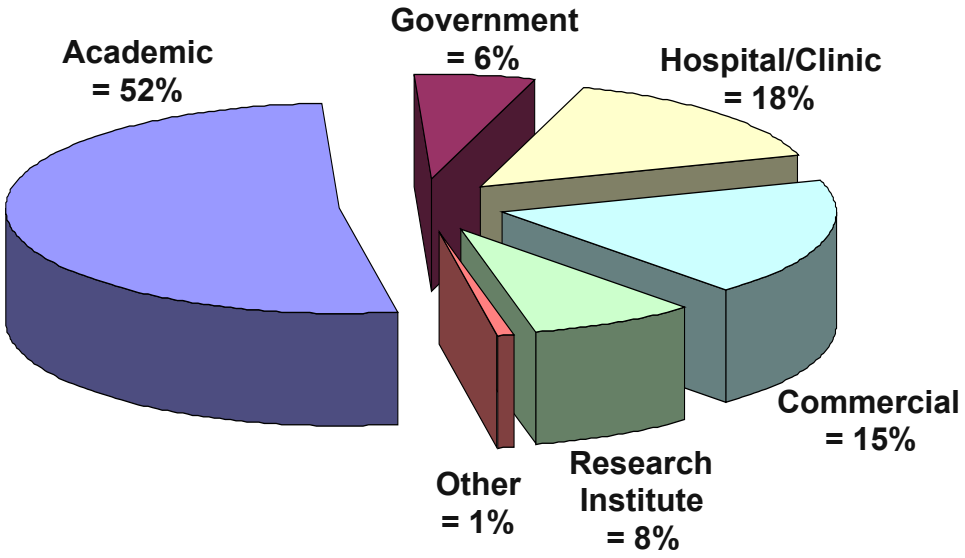
Register the IBC with OBA and file annual membership updates

- A roster of IBC members
  - Clearly indicate chair, contact person, and special expertise as appropriate (BSO, animal, plant, human gene transfer)
- Biographical sketches of all members

Purpose of registration and annual membership updates

- Provides assurance of local review of biosafety risks
- Allows OBA to see that IBC expertise consistent with the NIH Guidelines
- Indicates institutional point of contact
- Provides census of the field - where recombinant DNA research is being conducted

IBCs Registered with the NIH OBA
March 2005 – over 550 IBCs registered



IBC Responsibilities

Responsibilities

In basic and preclinical research, IBCs have authority to:

- Lower containment levels for certain experiments in which DNA 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

In a nutshell, what must IBCs review?

- Recombinant DNA research for conformity with the NIH Guidelines
- Potential risk to environment and public health

What do IBCs assess in reviewing recombinant DNA research?

- Containment levels per NIH Guidelines
- Adequacy of facilities, SOPs, PI and lab personnel training

Institutional and investigator compliance; e.g., adverse event reports

Restrictions

The IBC **MAY NOT**:

- Authorize initiation of rDNA experiments not explicitly covered by the NIH Guidelines until NIH (with the advice of the RAC when required) establishes the containment requirement.

IBCs and Exempt Research

Do IBCs determine what research is exempt? Does the PI?

- A matter of institutional policy – at Argonne all rDNA work is registered with the IBC
- IBC may wish to designate member, chair, or BSO as first line of review to make determinations about what is exempt and what requires full review
- NIH OBA can help with determinations

Meeting Minutes

Content of Minutes

- Not prescribed in the NIH Guidelines
- Generally accepted principles exist
    - Robert's Rules of Order
    - Need to document IBC fulfillment of review and oversight responsibilities
- Avoid extremes
    - Transcripts are probably not necessary
    - Don't simply state, "We met. We adjourned."
- Use good judgment and common sense

Convening an IBC

Section IV-B-2-a-(6) states:

"When possible and consistent with protection of privacy and proprietary interests, the institution is encouraged to open its Institutional Biosafety Committee meetings to the public."

- Institution has latitude in determining how to create public awareness of meetings
- Letter of the NIH Guidelines
  - IBCs are encouraged to open meetings to the public
  - Institution shall make IBC minutes available to the public upon request
- Intent of the NIH Guidelines
  - Interactive (face-to-face, video or teleconferencing)

Access to Minutes

- Section IV-B-2-a-(7) states:

Upon request, the institution shall make available to the public all Institutional Biosafety Committee meeting minutes and any documents[1] submitted to or received from funding agencies which the latter are required to make available to the public.

[1] Generally, rosters and biosketches

Access to Minutes

Redaction

- Section IV-B-2-a-(6) of the NIH Guidelines acknowledges that the protection of private or proprietary information is a basis for closing meetings to the public
- Since minutes are records of meetings, it is logical to extend protection of such information to minutes through redaction
- Redaction must be judicious and consistent

Forms of access

- Mail, e-mail, Web site (open or password protected)
- Requiring on-site inspection generally not appropriate
  - can be excessively burdensome on requestor
  - could be considered a deterrent

Special procedures

- Nothing in the NIH Guidelines precludes institutions from applying or complying with specific procedures in releasing minutes
- State institutions are often subject to state public disclosure laws; Federal facilities are subject to FOIA
- Following public disclosure laws is not inherently in conflict with the NIH Guidelines; reasonable fees to cover costs are acceptable

Training

The NIH Guidelines emphasize the importance of training and place responsibility on:

- Institutions to train IBC members, BSO, PI, and laboratory staff; and
- NIH to conduct and support training programs

Institutional Training Programs should:

- Provide information on federal requirements
- Include information on institutional policies, procedures, and requirements
- Be tailored to the audience – investigators vs. administrators vs. lab staff

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

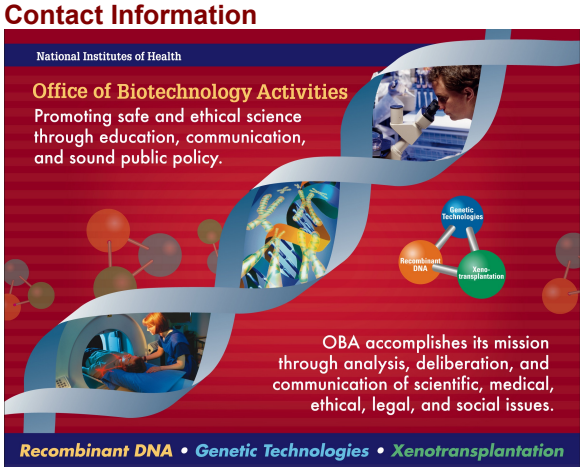
OBA Outreach and Education

Electronic communication tools

- Listserv: “OBA_NEWS”
  - Policy notices, meeting announcements, compliance reminders

- Email inbox for queries: oba@od.nih.gov
  - Questions on interpretation of the NIH Guidelines, status of protocols, scientific and medical issues

Contact Information



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