Overview of the Policy and Biosafety Framework for Human Gene Transfer Research: *The NIH Guidelines for Research Involving Recombinant DNA Molecules*
The Advent of Recombinant DNA Technology

- Emergence of recombinant DNA technology (mid-1970’s)
- Concerns among both scientific community and general public
  - Public health and safety
  - Environmental impact
  - Potential ethical and social implications
Policy Debate

- NAS Committee Report (July 1974); called for
  - A moratorium on certain experiments
  - Development of NIH guidelines for conduct and review of recombinant DNA experiments
  - An international conference
Asilomar Scientific Summit (1975)

- **Premise:**
  - Scientists taking responsibility for the risks of their own research activities

- **Outcomes**
  - Reaffirmation of the need for guidelines
  - Establishment of a new federal oversight committee
NIH Recombinant DNA Molecule Program Advisory Committee

- Launched process of developing NIH guidelines for recombinant DNA oversight
- Made recommendations about local oversight
  - Award NIH grants for recombinant DNA research only after review of risks by an institutional “biohazards” review committee
    - Review of physical containment and facilities
    - Consideration of local circumstances
The First NIH Guidelines

- Published in July 1976
- Established responsibilities of investigators and institutions
NIH Guidelines for Research Involving Recombinant DNA Molecules

- A scientifically-responsive document that will continue to evolve
- Have undergone multiple revisions since 1976
- Latest version - April 2002

Content of the *NIH Guidelines*

- Section I – Scope
- Section II – Safety Considerations
- Section III – Types of Experiments Covered
- Section IV – Roles and Responsibilities
- Appendices
NIH Guidelines – Section I

- **Scope and Applicability**
  - Specifies practices for constructing and handling
    - Recombinant DNA molecules
    - Organisms and viruses containing recombinant DNA molecules
  - **Definition**
    - 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
  - Applicability broader than many NIH grant requirements
The NIH Guidelines Apply to...

- Recombinant DNA research that is
  - 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
Are the NIH Guidelines optional?

- What are potential consequences of noncompliance with the NIH Guidelines?
  - 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.
Prescription versus Flexibility

- Some matters are left to institutional discretion

- Flexibility is a two-sided coin
  - Accommodates institutional diversity and heterogeneity
  - Can create uncertainty about expectations
“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
NIH Guidelines – Section II
### Safety Considerations

- **Risk assessments:** (Appendix B)

<table>
<thead>
<tr>
<th>RG 1</th>
<th>RG 2</th>
<th>RG 3</th>
<th>RG 4</th>
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</thead>
<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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</tbody>
</table>
NIH Guidelines – Section II

- Safety Considerations

- Containment
  - Physical (Appendix G)
    - Practices
    - Equipment/facilities
  - Biological (Appendix I)
    - Survival
    - Transmission
NIH Guidelines – Section III

IBC, RAC, NIH Director

IBC, OBA (in consult with experts)

IBC, IRB, RAC

IBC

IBC (notification)

Exempt
### NIH Guidelines - Section III
#### Levels of Review

<table>
<thead>
<tr>
<th>Level of review</th>
<th>Example of recombinant DNA research</th>
<th>Relevant section(s) of the NIH Guidelines</th>
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<tbody>
<tr>
<td>IBC, RAC review, and NIH Director review and approval - Major Action</td>
<td>Experiments that compromise the control of disease agents in medicine through deliberate transfer of a drug resistance trait</td>
<td>III-A</td>
</tr>
<tr>
<td>IBC approval and NIH review for containment determinations</td>
<td>Experiments conducted with a recombinant DNA modified restricted agent in a whole animal</td>
<td>III-B</td>
</tr>
<tr>
<td>IBC and IRB approval and NIH review before research participant enrollment</td>
<td>Experiments involving the deliberate transfer of recombinant DNA into a human research participant</td>
<td>III-C</td>
</tr>
<tr>
<td>IBC approval before initiation</td>
<td>Creating stable germline alterations of an animal’s genome, or testing viable recombinant DNA modified microorganisms on whole animals, where BL-2 containment or greater is necessary</td>
<td>III-D</td>
</tr>
<tr>
<td>IBC notice at initiation</td>
<td>Creating stable germline alterations of rodents using recombinant DNA when these experiments require only BL-1 containment</td>
<td>III-E</td>
</tr>
<tr>
<td>Exempt from the NIH Guidelines. IBC registration not required if experiment not covered by Sections III-A, III-B, or III-C</td>
<td>Purchase or transfer of transgenic rodents</td>
<td>III-F</td>
</tr>
</tbody>
</table>
NIH Guidelines – Section IV

- Roles and Responsibilities
  - Institution
  - Institutional Biosafety Committee (IBC)
  - Biological Safety Officer (BSO)
  - Principal Investigator (PI)
  - NIH
Institutional Responsibilities under the *NIH Guidelines*

- The Institution 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, PIs, laboratory staff
  - Determine necessity for health surveillance of personnel
  - Report any significant problems or violations to OBA within 30 days
The Principal Investigator shall (among other things):

- Initiate or modify no recombinant DNA research which requires IBC approval until approval is granted
- Determine whether experiments are covered under III-E 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 (on behalf of the NIH Director)

- 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
  - Certain basic recombinant DNA experiments
- “Minor actions”
  - Changes not requiring approval by the NIH Director
NIH Responsibilities under the NIH Guidelines

- 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
Appendix A – Exemptions: Natural Exchangers
Appendix B – Classification of Etiologic Agents
Appendix C – Exemptions under III-F
Appendix D – Major Actions
Appendix E – Certified Host-Vector Systems
Appendix F – Biosynthesis of Toxic Molecules
Appendix G – Physical Containment
Appendix H – Shipment
Appendix I – Biological Containment
NIH Guidelines - Appendices

- Appendix J – Biotechnology Research Subcommittee
- Appendix K – Large Scale Physical Containment
- Appendix L – Gene Therapy Policy Conferences
- Appendix M – Points to Consider in Human Gene Transfer Research
- Appendix P – Physical and Biological Containment: Plants
- Appendix Q – Physical and Biological Containment: Animals
Appendix B

- Classification of human etiologic agents on the basis of hazard
  - Bacterial
  - Fungal
  - Virus
  - Prion
  - Parasites
Appendix G

- Specifies details of containment and confinement for standard laboratory practices
- Defines Biosafety Level 1 through Biosafety Level 4
- Appropriate for animals that are worked with in a laboratory setting
Appendix I

- Biological containment barriers
  - Limit the infectivity of a vector or vehicle (plasmid or virus) for specific hosts
  - Limit dissemination and survival of a vector in the environment

- Vectors can be genetically designed to decrease, by many orders of magnitude, the probability of dissemination of recombinant DNA outside the laboratory
Appendix M

- Points to Consider in the design and submission of protocols for the transfer of recombinant DNA Molecules into one or more human research participants.
  - Requirements for Protocol Submission, Review, and Reporting
Appendix Q

- Applies when research animals are of a size or have growth requirements that preclude laboratory containment
  - For example, cattle, swine, sheep, goats, horses, poultry, etc.
- Addresses containment and confinement practices in animal facilities (BL1-N to BL4-N)
NIH OBA provides oversight, guidance, and resources

- Staff and information resources available to help ensure investigators and their institutions are compliant with the *NIH Guidelines*

- Scientific and medical staff available to answer queries
  - Interpretation of *NIH Guidelines*
  - Containment
  - Exemptions
  - Risk group classification
Institutional Biosafety Officer
Institutional Biosafety Committee

Lab Safety Issues

- Personal protective equipment for personnel
- Disposal of waste
- Decontamination of laboratory and equipment
- Containment facilities
- Accidents (emergency plans and response)
Questions?