

# NIH Guidelines for Research Involving Recombinant DNA

Biosafety and the Emerging Technology of  
Synthetic Biology

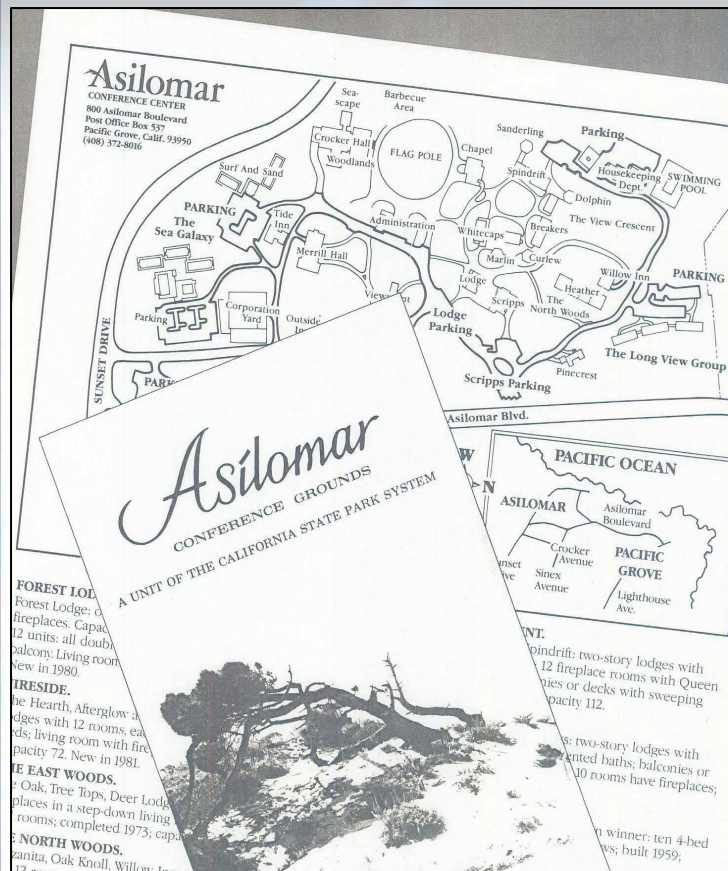


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# A Brief History of Recombinant DNA Oversight



## □ 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**

# A Brief History of Recombinant DNA Oversight

- **NIH Recombinant DNA Advisory Committee (RAC)**
  - **Launched process of developing NIH guidelines for recombinant DNA oversight**
  - **Made recommendations about local oversight – Institutional Biosafety Committees**
  - **Continues to advise the NIH Director on rDNA research, both basic and clinical (human gene transfer)**

# National Science Advisory Board for Biosecurity Report

NATIONAL  
SCIENCE  
ADVISORY  
BOARD FOR  
BIOSECURITY

ADDRESSING BIOSECURITY CONCERNS  
RELATED TO THE SYNTHESIS OF  
SELECT AGENTS

DECEMBER 2006



# National Science Advisory Board for Biosecurity

- ❑ **National Science Advisory Board for Biosecurity (NSABB) chartered by U.S. Government.**
- ❑ **Advisory to HHS Secretary, NIH Director, and heads of all Federal entities that conduct/support life sciences research.**
- ❑ **Is staffed and administered by the Office of Biotechnology Activities.**

# **NSSAB Finding on Synthetic Genomics and Biosafety**

- ❑ Some practitioners of synthetic genomics are:**
  - Educated in disciplines that do not routinely entail formal training in biosafety; and**
  - Uncertain about when to consult an Institutional Biosafety Committee (IBC).**
- ❑ Ensure that biosafety principles and practices are applicable to synthetic genomics and easily understood.**

# Current Biosafety Guidance

- ***NIH Guidelines for Research Involving Recombinant Molecules (NIH Guidelines)***
  - Applies to institutions that receive NIH funding for recombinant DNA research as term and condition of grant
  - Other government agencies also require adherence, e.g. Department of Defense
  
- **CDC/NIH Biosafety in Microbiological and Biomedical Laboratories Manual (BMBL)**
  - Agent specific, not technology driven
  - References *NIH Guidelines* with respect to recombinant molecules

# Implementation of Recommendation by U.S. Government

- NSABB recommendations were considered through a trans-federal policy coordination process
  - Led by the White House Homeland Security Council and Office of Science and Technology Policy
- Recommendation on need for biosafety guidance accepted by U.S. Govt. with understanding that implementation would be through modification of *NIH Guidelines* as appropriate and referenced in the BMBL



# Definition of Recombinant DNA

## □ *NIH Guidelines*

- Molecules that are constructed outside living cells by joining natural or **synthetic DNA** segments to DNA molecules that can replicate in a living cell, or
- Molecules that result from the replication of those described above

# Definition of Recombinant DNA

- ***NIH Guidelines* are limited to synthetic DNA joined by recombinant methods**
  - Does not cover synthetic DNA that is synthesized *de novo*
  - Does not cover synthesized RNA viruses

# Scope of the *NIH Guidelines*

- ❑ **Basic research with nucleic acids (NAs) that are in cells, viruses or organisms**
  - **Does not cover just synthesis of NAs**
- ❑ **Transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into one or more human subjects**

# Charge to the Recombinant DNA Advisory Committee

- ❑ **Consider the application of the *NIH Guidelines* to synthetic biology**
  - To what degree is this technology covered?
  - Does the scope need to be modified to capture synthetic biology research?
- ❑ **Develop draft recommendations regarding principles and procedures for risk assessment and management of research involving synthetic biology**

# Review Process to Date

- ❑ Initial proposal developed by a sub-group of the RAC, the Biosafety Working Group
- ❑ Proposed revisions reviewed and approved by full RAC in March 2008
- ❑ Proposal in Federal Register on March 4, 2009 with opportunity for public comment (74 FR 9411)
- ❑ Stakeholders' Conference, June 23, 2009  
Arlington VA

<http://oba.od.nih.gov/rdna/rdna.html>

# Overarching Themes

- ❑ Capture the same products made by synthetic techniques that are currently covered under the *NIH Guidelines* for recombinant DNA research, provided the same biosafety concerns are raised
  - **Level of review based on risk, not technique**
- ❑ Develop a risk management framework that is based on the current science and what appears to be feasible in the foreseeable future
- ❑ Not all future scientific developments can be anticipated; the *NIH Guidelines* will need periodic review and updating

# Section I-B. Proposed Definition of Recombinant DNA Molecules

In the context of the *NIH Guidelines*, recombinant and synthetic nucleic acids are defined as:

(i) Recombinant nucleic acid molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell,

(ii) **Synthetic nucleic acid molecules that are chemically, or by other means, synthesized or amplified nucleic acid molecules that may wholly or partially contain functional equivalents of nucleotides, or**

(iii) molecules that result from the replication of those described in (i) or (ii) above.

# Replication: a Unique Risk Characteristic

- ❑ **The ability to replicate is one of the unique risks of recombinant DNA molecules and is part of definition**
  - Potential ability to propagate in the lab, in exposed laboratory workers, and the environment
- ❑ **Are the risks of non-replicating synthetic molecules comparable?**
  - For basic research
  - For clinical research



# Basic, Non-Clinical Research with Synthetic Nucleic Acids that cannot Replicate

- New proposed Section F-1 exempts from the *NIH Guidelines* synthetic nucleic acids that cannot replicate, provided not used in human gene transfer
  - Exemption of non-replicating NA is consistent with current *NIH Guidelines* for laboratory rDNA research
    - Limited to molecules that can replicate or are derived from such molecules
  - Exemption will not apply to non-replicating synthetic NA used in human gene transfer
    - Difference based on likely increased risk from deliberate human gene transfer compared to inadvertent lab exposure

# Risk of Non-replicating Synthetic NAs: Basic Research

- ❑ **Exposure in the lab to a low dose of non-replicating synthetic nucleic acid sequence is considered low risk**
  - Limited because even if the NAs enter a cell can not replicate and spread
  - Could not spread in the environment if escaped
  - Exposure similar to that of a chemical exposure; however nucleic acids are not toxic in and of themselves

# Risks in Human Gene Transfer

- ❑ Doses used in human gene transfer extremely high compared to that expected for inadvertent lab exposure
- ❑ Many human gene transfer trials use replication incompetent vectors. However, safety risks due to transgene effects, insertional mutagenesis, and immunological responses are independent of the replicative nature of the vector
- ❑ Human gene transfer raises unique scientific, medical and ethical issues that warrant transparent oversight

# Questions Posed to Scientific Community

- ❑ Are there examples of non-replicating, synthetic NA research that should not be exempt due to increased risk, e.g. expression cassettes for **toxins or oncogenes**?
- ❑ For **human gene transfer** are the classes of experiments that use non-replicating NA that should be exempt due to lower potential risk (e.g. antisense RNA, or RNAi?)

# **RISK ASSESSMENT UNDER THE *NIH GUIDELINES***

**DOES THE SAME FRAMEWORK APPLY?**

# Risk Groups (RG) Under the *NIH Guidelines*

- **RG1** Agents that are not associated with disease in healthy adult humans
- **RG2** Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available
- **RG3** 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)
- **RG4** Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions *are not usually* available (high individual risk and high community risk)

**Containment Level (Biosafety Level) may be raised or lowered depending on a comprehensive risk assessment.**

# Risk Assessment under the *NIH Guidelines*

- ❑ Starting point for the Risk Assessment (RA) is the non-recombinant “parent” organism
- ❑ Containment may be raised or lowered depending upon the recombinant agent factors and manipulation:
  - Virulence
  - Pathogenicity
  - Infectious Dose
  - Environmental stability
  - Route of Spread
  - Communicability
  - Operations
  - Quantity
  - Availability of vaccine or treatment
  - Gene product effects:
    - Toxicity
    - Physiologic activity
    - Allergenicity

# Proposed Risk Assessment for Synthetic NAs

- **RA is not fundamentally different; however**
  - As the technology moves forward, chimeras may be generated for which the parent organism is not obvious
    - RA should consider the organism(s) from which the sequences were derived and the function of those sequences
    - It may be prudent to first consider the highest risk group classification of any agent sequence in the chimera



# Proposed Risk Assessment for Synthetic NAs

- **Other factors to be considered:**
  - % of genome contributed by each of multiple parent agents
  - Predicted function or intended purpose of each sequence
- Assume the sequence will function as does in the original host
- Consider the possibility that synergism between sequences and transgenes may result in an organism whose risk profile is higher than that of the contributing sequences or organisms

# The “Spirit Clause”: Section IV Policy

- The safe conduct of experiments involving recombinant **or synthetic nucleic acids** depends on the individual conducting such activities. The *NIH Guidelines* cannot anticipate every possible situation. Motivation and good judgment are the key essentials to protection of the health and environment. The NIH Guidelines are intended to assist the Institution, IBC, Biological Safety Officer, the Principle Investigator in determining safeguards that should be implemented. The *NIH Guidelines* will never be complete or final since all conceivable experiments involving recombinant **or synthetic nucleic acids** cannot be foreseen.

# The Spirit Clause: Section IV Policy Proposed Additions

- ❑ Utilization of new genetic manipulation techniques may enable work previously done by recombinant means to be accomplished faster, more efficiently or at larger scale.
- ❑ Techniques have not yet yielded organisms that present safety concerns that fall outside the current RA framework used for recombinant DNA research.
- ❑ As the field develops new techniques and applications, the NIH Guidelines may need to be updated.

# Conclusions

- ❑ Research with synthetic NAs in most cases present biosafety risks that are comparable to rDNA research
- ❑ The current RA framework can be used with attention to the unique aspects of this technology
- ❑ Certain work with non-replicating synthetic NAs may not require oversight under the *NIH Guidelines* although other biosafety standards will apply