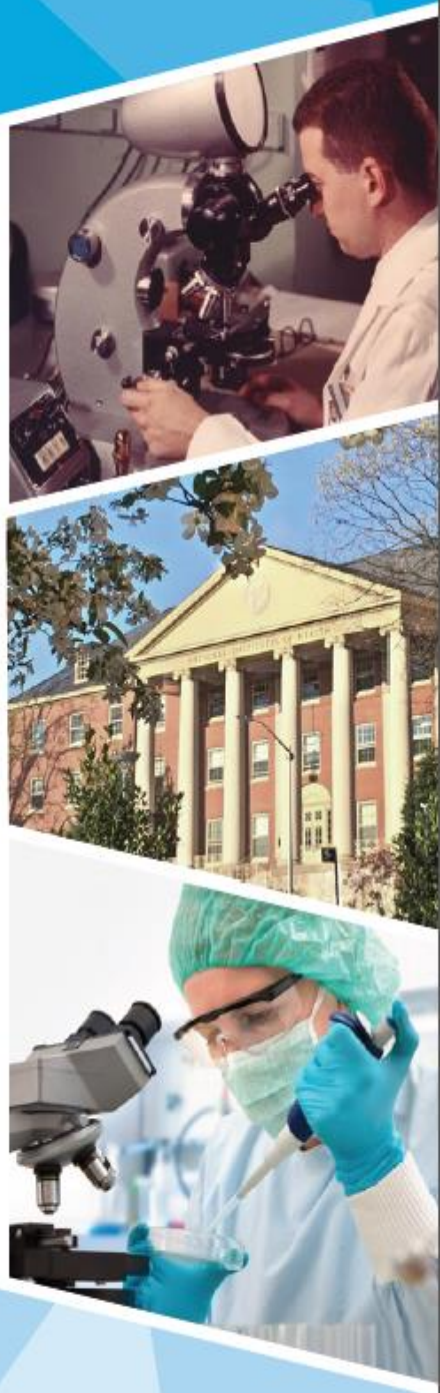
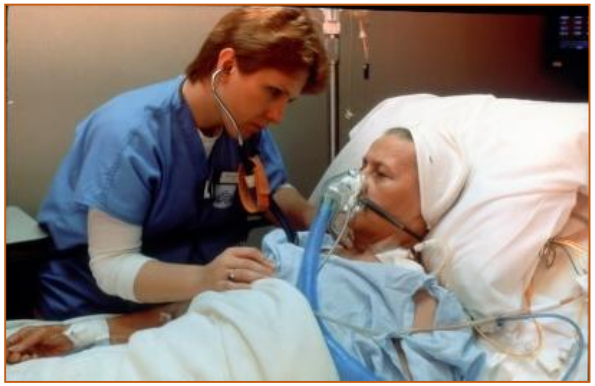
NIH Guidelines: Honoring the Past, Charting the Future



Welcome

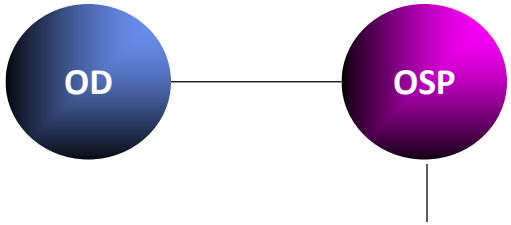
The National Institutes of Health

Science in pursuit of fundamental knowledge about the nature and behavior of living systems…and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.



NIH Office of Science Policy

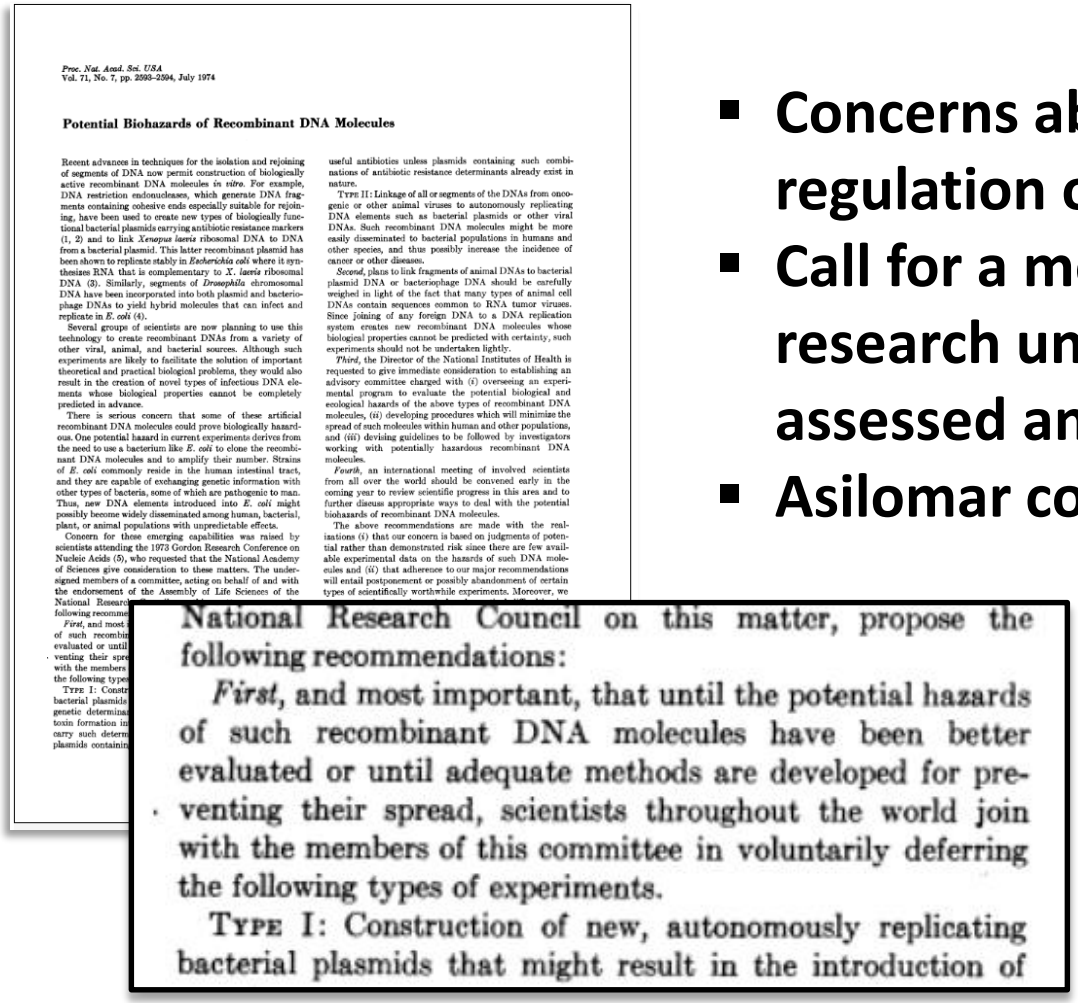
- **Advise the NIH Director on matters of significance to the agency, the research community, and the public**
- **Promote progress in the biomedical research enterprise through the development of sound and comprehensive policies**
- **Foster dialog on emerging policies that affect the biomedical research community**



- Biosafety, Biosecurity, and Emerging Biotechnology Policy Division
- Scientific Data Sharing Policy Division
- Science Policy Coordination, Collaboration, and Reporting Division
- Technology Transfer and Innovation Policy Division
- Clinical and Healthcare Research Policy Division

Asilomar

Advent of Recombinant DNA Technology



Proc. Nat. Acad. Sci. USA
Vol. 71, No. 7, pp. 2593–2594, July 1974

Potential Biohazards of Recombinant DNA Molecules

Recent advances in techniques for the isolation and rejoining of segments of DNA now permit construction of biologically active recombinant DNA molecules *in vitro*. For example, DNA restriction endonucleases, which generate DNA fragments containing cohesive ends especially suitable for rejoining, have been used to create new types of biologically functional bacterial plasmids carrying antibiotic resistance markers (1, 2) and to link *Xenopus laevis* ribosomal DNA to DNA from a bacterial plasmid. This latter recombinant plasmid has been shown to replicate stably in *Escherichia coli* where it synthesizes RNA that is complementary to *X. laevis* ribosomal DNA (3). Similarly, segments of *Drosophila* chromosomal DNA have been incorporated into both plasmid and bacteriophage DNAs to yield hybrid molecules that can infect and replicate in *E. coli* (4).

Several groups of scientists are now planning to use this technology to create recombinant DNAs from a variety of other viral, animal, and bacterial sources. Although such experiments are likely to facilitate the solution of important theoretical and practical biological problems, they would also result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance.

There is serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous. One potential hazard in current experiments derives from the need to use a bacterium like *E. coli* to clone the recombinant DNA molecules and to amplify their number. Strains of *E. coli* commonly reside in the human intestinal tract, and they are capable of exchanging genetic information with other types of bacteria, some of which are pathogenic to man. Thus, new DNA elements introduced into *E. coli* might possibly become widely disseminated among human, bacterial, plant, or animal populations with unpredictable effects.

Concern for these emerging capabilities was raised by scientists attending the 1973 Gordon Research Conference on Nucleic Acids (5), who requested that the National Academy of Sciences give consideration to these matters. The undersigned members of a committee, acting on behalf of and with the endorsement of the Assembly of Life Sciences of the National Research Council on this matter, propose the following recommendations:

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring the following types of experiments.

TYPE I: Construction of new, autonomously replicating bacterial plasmids that might result in the introduction of useful antibiotics unless plasmids containing such combinations of antibiotic resistance determinants already exist in nature.

TYPE II: Linkage of all or segments of the DNAs from oncogenic or other animal viruses to autonomously replicating DNA elements such as bacterial plasmids or other viral DNAs. Such recombinant DNA molecules might be more easily disseminated to bacterial populations in humans and other species, and thus possibly increase the incidence of cancer or other diseases.

Second, plans to link fragments of animal DNAs to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed in light of the fact that many types of animal cell DNAs contain sequences common to RNA tumor viruses. Since joining of any foreign DNA to a DNA replication system creates new recombinant DNA molecules whose biological properties cannot be predicted with certainty, such experiments should not be undertaken lightly.

Third, the Director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules, (ii) developing procedures which will minimize the spread of such molecules within human and other populations, and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

The above recommendations are made with the realizations (i) that our concern is based on judgments of potential rather than demonstrated risk since there are few available experimental data on the hazards of such DNA molecules and (ii) that adherence to our major recommendations will entail postponement or possibly abandonment of certain types of scientifically worthwhile experiments. Moreover, we

- **Concerns about biohazards and the regulation of biotechnology**
- **Call for a moratorium on rDNA research until safety issues were assessed and recommendations made**
- **Asilomar conference**

Proc Natl Acad Sci U S A. 1974 Jul; 71(7): 2593–2594

Asilomar ‘75:
The Beginning of the Future

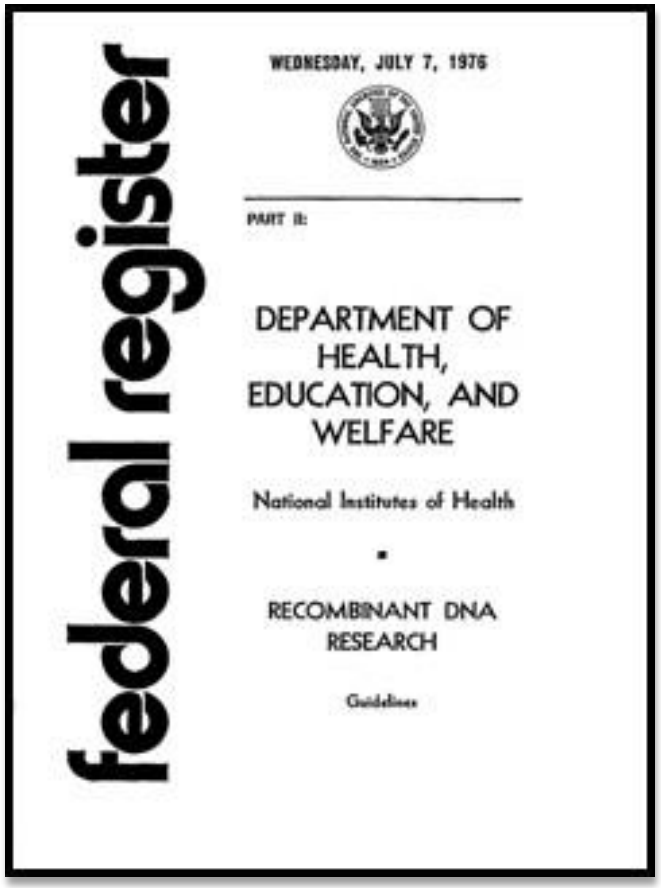
Establishment of the Recombinant DNA Advisory Committee

- **1974 - NIH Director Dr. Donald Fredrickson forms RAC in response to concerns raised about the risks of recombinant DNA experimentation**
- **1975 - Members of the RAC began writing the *NIH Guidelines for Research Involving Recombinant DNA Molecules* after the landmark Asilomar conference**

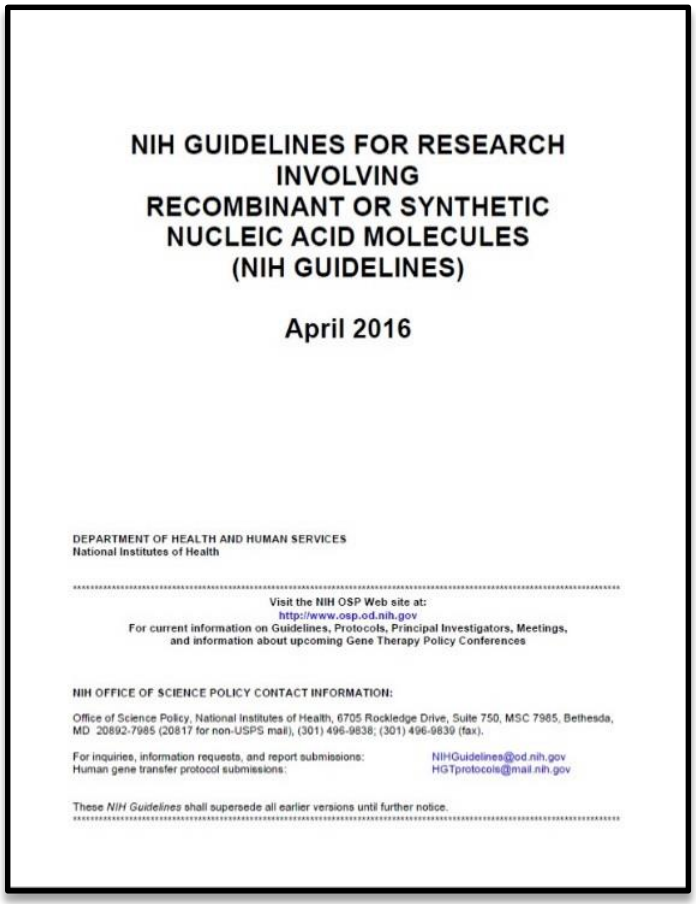
- **1976 – First *NIH Guidelines* published in the Federal Register**

Development of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*

- **Founding principles:**
  - **Responsible conduct of research**
  - **Development of a transparent biosafety governance framework**
- **Enabled advances in the life sciences while promoting the safety of researchers, the public, and the environment**



NIH Guidelines Today



NIH GUIDELINES FOR RESEARCH
INVOLVING
RECOMBINANT OR SYNTHETIC
NUCLEIC ACID MOLECULES
(NIH GUIDELINES)

April 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Visit the NIH OSP Web site at:
http://www.osp.od.nih.gov
For current information on Guidelines, Protocols, Principal Investigators, Meetings, and information about upcoming Gene Therapy Policy Conferences

NIH OFFICE OF SCIENCE POLICY CONTACT INFORMATION:

Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), (301) 496-9838; (301) 496-9839 (fax).

For inquiries, information requests, and report submissions: NIHGuidelines@od.nih.gov
Human gene transfer protocol submissions: HGTprotocols@mail.nih.gov

These *NIH Guidelines* shall supersede all earlier versions until further notice.

- **Framework of oversight for research with recombinant, and synthetic, nucleic acid molecules at institutions funded by the NIH**
- **A scientifically-responsive document that has evolved with scientific advances**
  - **Amended multiple times since 1976**
  - **Latest version – April 2016**

Workshop Impetus: We've come a long way, baby!

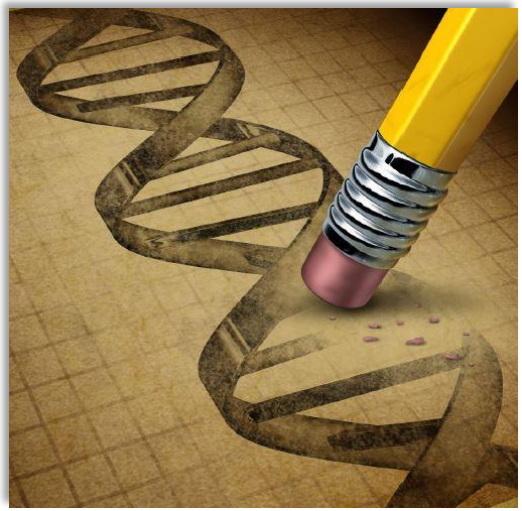
- Recent 40 year anniversary of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*

- Emergence of new biotechnology capabilities in the life sciences - synthetic biology, genome editing tools etc.

- Ensure our biosafety oversight system retains its currency for assessing and managing risks as the scientific landscape continues to evolve

Why are we spending the next two days together?

- What has history taught us and analogies for today
- Current landscape of oversight inside and outside the *NIH Guidelines*
- Emerging biotechnologies:
  - Unique biosafety (as opposed to ethical/security) challenges?
  - Frameworks for risk assessment and management?



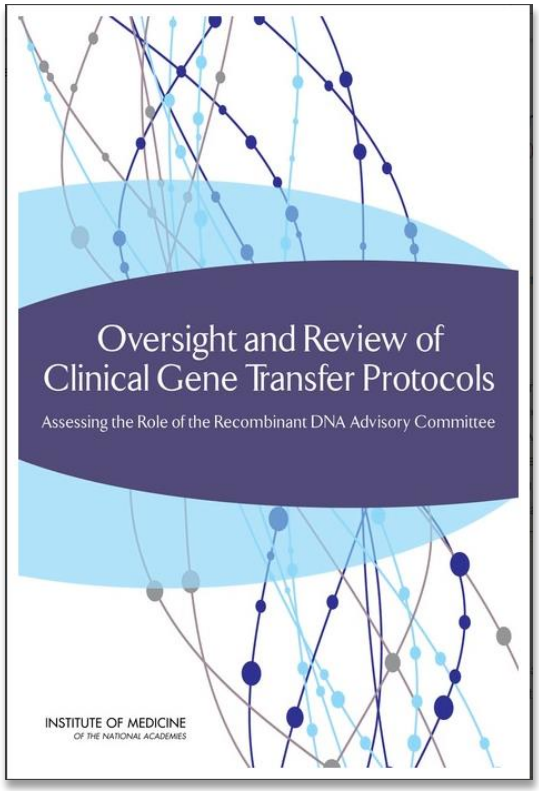
Discuss!

Provide an opportunity for stakeholders to provide input to NIH on a path forward in considering potential revisions to the *NIH Guidelines*

- **What should be captured in our biosafety oversight system?**
- **Whether additional biosafety guidance is needed?**
- **How do we ensure our oversight system will evolve with fast with rapidly emerging technologies while allowing science to proceed safely and responsibly?**
- **What is future role of the *NIH Guidelines* within the context of the biosafety oversight system in the U.S., and the role of the RAC within this system?**

And speaking of the RAC….

Evolution of the RAC – Oversight of Human Gene Transfer Research



Institute Of Medicine Study (2014)

- **NIH requested independent review and assessment to**
  - **Determine if human gene transfer research (HGT) raises issues of concern that warrant extra oversight by the RAC of individual clinical trial protocols involving gene transfer techniques**
  - **Recommend criteria to guide when the RAC should review HGT research**

IOM Recommendations and NIH Response

"The RAC has successfully provided oversight over a complex technology for nearly 40 years, providing a valuable service to NIH, the scientific community, and to the public."

- **IOM recommendations:**
  - **Restrict individual gene transfer protocol reviews to exceptional cases that meet specified criteria**
  - **Consider integrating oversight for gene transfer and other applications of emerging technologies**

- **NIH response**
  - **Amended *NIH Guidelines* April 27, 2016**

Agenda Overview - Day 1

- Keynote Address
- The Current NIH Framework for the Oversight of Research with Recombinant or Synthetic Nucleic Acid Molecules
- Role of the *NIH Guidelines*: Intersection with Other Biosafety Regulations and Guidance
- Emerging Biotechnologies: Issues Raised for the Current System of Biosafety Oversight

Agenda Overview - Day 2

- **Roundtable Discussions:**
  - **Future Role of the RAC**
  - **Future Face of Biosafety Oversight**

- **Discussions will be lead by expert moderators**
- **Three main themes for each round table**
  - **Discussion questions in your workshop materials package**
- **Audience participation welcome and strongly encouraged!**
  - **Round tables and Open Forum**
  - **Please use microphones when posing questions and providing comments**

Who knows… someday?

Bethesda North Marriott Hotel & Conference Center

Ashonmar