NATIONAL INSTITUTES OF HEALTH
PUBLIC CONSULTATION
SYNTHETIC NUCLEIC ACIDS AND THE
NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

Hyatt Regency Crystal City
Arlington, Virginia

June 23, 2009
8:30 am – 5:30 pm

***Agenda**

8:30 am **Welcome and Opening Remarks**

- Amy Patterson, M.D.
  Acting Director, Office of Science Policy, National Institutes of Health (NIH), Bethesda, MD
- Howard Federoff, M.D., Ph.D.
  Recombinant DNA Advisory Committee Chair and Executive Vice President and Dean, Georgetown University Medical Center, Washington, DC

8:45 am **Introduction to the Proposed Revisions to the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)***

- Stephen Dewhurst, Ph.D.
  University of Rochester Medical Center, Rochester, NY

9:00 am **Panel I – Basic Research Involving Synthetic Nucleic Acids**

Co-moderators:

- Claudia Mickelson, Ph.D.
  Massachusetts Institute of Technology, Cambridge, MA
- Jane Flint, Ph.D.
  Princeton University, Princeton, NJ

Background

Section I-B Basic Research with Recombinant and Synthetic Nucleic Acids
The proposed revisions to the *NIH Guidelines* are intended to clarify the applicability of the *NIH Guidelines* to research with synthetic nucleic acids and provide principles and procedures for risk assessment and management of such research. Although synthetic biology utilizes different techniques than traditional recombinant methods, the ultimate product may be the same. The biosafety considerations in most cases are related to the product being produced more than the technique used. Synthetic nucleic acids that cannot replicate will be exempted from the *NIH Guidelines* unless they are used in human gene transfer (see Section III-C-1 of the *NIH Guidelines*). This exemption is proposed so that the *NIH Guidelines* apply to synthetic nucleic acid research in a manner consistent with the current oversight of basic and preclinical recombinant DNA research. Currently oversight is limited to recombinant molecules that replicate or are derived from such molecules. The biosafety risks of using such constructs in basic and preclinical research are believed to be low. In contrast, the risks of administering non-replicating synthetic nucleic acids in the clinical setting are considered equivalent to those with replication incompetent vectors and this research is not exempted.

Discussion Questions

1. Is there a sufficient distinction between the risks of basic and preclinical research with replicating vs. non-replicating synthetic molecules to warrant the exemption?
   – What are the risks with the use of replication incompetent integrating vectors in the laboratory? At the lower doses typically used in laboratory experiments, are the risks to the laboratory worker of such non-replicating, synthetic nucleic acid research sufficiently low as to warrant exemption from the *NIH Guidelines*?

2. Since the increased risk associated with human gene transfer is in part related to the administration of higher doses, should the exemption be limited to experiments involving the handling of low quantities or doses of nucleic acids? What quantity would be expected not to pose a biosafety risk?

3. Are there examples of non-replicating, synthetic nucleic acid research that should not be exempt due to greater potential risks (e.g., expression cassettes for oncogenes or toxins)?

4. Do the proposed changes to the Risk Assessment adequately address the potential risks for synthetic biology?

Panel Discussion

Institutional Biosafety Committee

- Carolyn Keierleber, Ph.D.
  The Scripps Research Institute, La Jolla, CA
- Richard Stephens, Ph.D., M.S.P.H.
  University of California, Berkeley, CA

Academic Investigator

- Drew Endy, Ph.D.
  Stanford University, Stanford, CA
- John Glass, Ph.D.,
  Synthetic Biology Group, *Venter Institute, Rockville, MD*
- Kristala Jones Prather, Ph.D.
  Massachusetts Institute of Technology, Cambridge, MA

Public Comment

11:00 am **BREAK**

11:15 am **Panel II – Human Gene Transfer Research Involving Synthetic Nucleic Acids**

Moderator:

- Howard Federoff, M.D., Ph.D.
  Georgetown University, Washington, DC

Background

Currently human gene transfer experiments involving non-replicating recombinant molecules are captured by the *NIH Guidelines* when derived through recombinant technology that has steps involving replication (e.g., replication incompetent vectors, RNAi or antisense RNA expressed from vectors derived from replicating systems). The potential safety risks for human gene transfer with synthetic non-replicating nucleic acids are not fundamentally different than for non-replicating recombinant vectors. The distinction between laboratory research and human gene transfer for non-replicating synthetic nucleic acids is based on the difference in the potential health risk between inadvertent exposure during basic or preclinical work and deliberate clinical gene transfer. The doses and routes of administration used in human gene transfer increase the risks. The risks to be considered for human gene transfer are not limited to the ability of the vector to replicate, and include transgene effects, insertional mutagenesis, and unanticipated immunological responses. Human gene transfer also raises scientific, medical, social and ethical considerations that warrant special attention and public discussion.

Discussion Questions

1. For human gene transfer research, are there classes of non-replicating synthetic molecules that should be exempt from the *NIH Guidelines* due to lower potential risks (e.g., antisense RNA, RNAi, etc.)?

2. If so, what criteria should be applied to determine such classes?

Panel Discussion

Institutional Biosafety Committee

- Edouard Cantin, Ph.D.
  City of Hope, Duarte, CA
- Henry V. Huang, Ph.D.
  Washington University School of Medicine, Saint Louis, MO

Academic Investigator

- Scott Q. Harper, Ph.D.
  Nationwide Children's Hospital, Columbus, Ohio
- Phillip Zamore, Ph.D.
  University of Massachusetts Medical School, Worcester, MA

Industry Investigator

- Richard Geary, Ph.D.
  Isis Pharmaceuticals, Carlsbad, CA
- Akshay K. Vaishnaw, M.D., Ph.D.
  Alnylam Pharmaceuticals, Inc., Cambridge, MA

Public Representation

- Terry Kwan, M.S.Ed
  Brookline, MA

Public Comment

12:30 pm **LUNCH**

1:15 pm **Panel II – *Continued***

2:15 pm **BREAK**

2:30 pm **Panel III – Revisions to Section III-A-1. Major Actions Under the *NIH Guidelines***

Co-moderators:

- Louis Kirchhoff, M.D.
  University of Iowa, Iowa City, IA
- Dennis Dixon, Ph.D.
  National Institutes of Allergy and Infectious Diseases, NIH, Bethesda, MD

Background

Section III-A-1-a

Under the *NIH Guidelines*, certain experiments involving the deliberate transfer of a drug resistance trait to microorganisms, if such acquisition could compromise the ability to treat or manage disease agents in human and veterinary medicine, or agriculture, must be reviewed by RAC and approved by the NIH Director. In the current *NIH Guidelines*, if the microorganism is "known to acquire the trait naturally", then transfer of the drug resistance does not need to be reviewed. The proposal would delete this language because a microorganism's ability to acquire the trait naturally may not be determinative of the safety and public health implications of the research. In addition, some in the research community have erroneously interpreted this section as applying only when the drug resistant trait is against first-line treatments. Therefore, the revised section clarifies that even if an alternative drug or drugs exist for the control or management of disease, it is important to consider how use of the drug resistance marker might affect the ability to control infection by resistant microorganisms in certain groups or subgroups for which alternative treatments may not be readily available. Affected groups or subgroups may include, but are not limited to: children, pregnant women, and people who are either allergic to effective alternative treatments, immunocompromised or living in countries where the alternative effective treatment is not readily available.

Discussion Questions

1. Does the amended language provide sufficient guidance as to which experiments should receive this heightened review?

2. Does the removal of the phrase "not known to acquire the trait naturally" inappropriately expand that potential number of experiments that would now require RAC review and NIH Director approval?

3. Are there other objective criteria that could be used to better capture those experiments that have potentially significant public health implications?

4. Alternatively, does the risk assessment require analysis that is specific to the organism, type of disease and the available therapeutics such that a case by case approach to determine whether review is needed is most appropriate?

Panel Discussion

Institutional Biosafety Committee
- Andrew B. Onderdonk, Ph.D.
  Harvard Medical School, Boston, MA

Principal Investigator
- Ron Atlas, Ph.D.
  University of Louisville, Louisville, KY
- William R. Bishai, M.D., Ph.D.
  Johns Hopkins School of Medicine, Baltimore, MD
- Stanley Maloy, Ph.D.
  San Diego State University, San Diego, CA
- Louis Rice, M.D.
  Case Western Reserve University, Cleveland, OH

Public Comment

4:00 pm **BREAK**

4:10 pm **Panel IV – Revisions to Section III-E-1. Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than One-Half of the Genome of any Eukaryotic Virus**

Co-moderators:
- Stephen Dewhurst, Ph.D.
  University of Rochester School of Medicine and Dentistry
- Bernard Roizman, Sc.D.
  The University of Chicago, Chicago, IL

Background

Section III-E-1
Under the current *NIH Guidelines*, tissue culture experiments with viruses (with all viruses from a single family being considered identical) containing < 2/3 of the genome can be initiated at Biosafety level (BL) 1 upon registration with the Institutional Biosafety Committee. Concerns were raised that this level of oversight may not be adequate for research with potential synthetic biology agents derived from multiple segments of nucleic acid from a family of viruses. In addition, some wild type viruses may be functional with less than 2/3 of the genome present. Therefore, a recommendation was made to propose changing the 2/3 of the genome criteria to 1/2 of the genome to reflect the current understanding of the biology of certain viruses. Since under Appendix C-1, recombinant molecules from Risk Group 1 and 2 viruses that contain less than 1/2 of any eukaryotic genome are exempt from the *NIH Guidelines*, the revised section would only apply to tissue culture work with Risk Group 3 and 4 viruses containing less than 1/2 of the genome. In addition, the new section requires that the principal investigator must provide evidence that the preparation(s) are free of replication competent virus.

Discussion Questions

1. Is the reduction from 2/3 to 1/2 the genome appropriate more appropriate from a biosafety perspective or are there many experiments involving Risk Group 3 or 4 viruses which contain more than 1/2 of the genome but less than 2/3 that can safely be done at BL1?

2. As this section allows initiation of the experiment simultaneously with IBC registration, is the requirement to obtain evidence that the resulting nucleic acid in these cells are not replication competent nucleic acids sufficiently clear that it could be implemented by Principal Investigators in a consistent manner?

5:10pm **Wrap-up and Concluding Remarks**

- Howard Federoff, M.D., Ph.D.

5:30 pm **ADJOURNMENT**

*draft agenda as of 04/23/09