NIH Guidelines for Research Involving Recombinant DNA

Biosafety and Synthetic Nucleic Acids

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NSABB Recommendation 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

Definition of Recombinant DNA

- Current *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

Scope of the *NIH Guidelines*

- ***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**

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
- Final Proposal Submitted RAC meeting December 1, 2009

RAC Biosafety Working Group Roster

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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. Revised Proposed Definition

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, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, or
(iii) molecules that result from the replication of those described in (i) or (ii) above.

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

- **New proposed Section F-1 exempts from the *NIH Guidelines* certain 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 all 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 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 (RA) 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 organisms 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
      - 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

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**