

# **Synthetic Nucleic Acids and the *NIH Guidelines for Research Involving Recombinant DNA***

## **Panel II**

### **Human Gene Transfer Research Involving Synthetic Nucleic Acids**

**Howard Federoff, M.D., Ph.D.**

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# **Panel II: Human Gene Transfer and Synthetic Nucleic Acids**

## **Panelists**

**Peter Besmer, Ph.D.  
Memorial Sloan-Kettering  
Cancer Center**

**Edouard Cantin, Ph.D.  
City of Hope**

**Henry Huang, Ph.D.  
Washington University School  
of Medicine**

**Scott Harper, Ph.D.  
Nationwide Children's Hospital**

**Phillip Zamore, Ph.D.  
University of Massachusetts  
Medical School**

**Richard Geary, Ph.D.  
Isis Pharmaceuticals, Inc.**

**Akshay K. Vaishnaw, M.D., Ph.D.  
Washington University School of  
Medicine**

**Terry Kwan, M.S. Ed.  
Public Representative  
and former RAC member**

# Risks in Human Gene Transfer

- ❑ Doses used in human gene transfer trials are deliberately high compared to those typically used in the lab
- ❑ Many human gene transfer trials use replication incompetent vectors; however, known safety risks are due to transgene effects, insertional mutagenesis, and immunological responses - these are independent of vector replication
- ❑ Human gene transfer raises unique scientific, medical and ethical issues that warrant special oversight

# Discussion Questions

- Potential advantages of non-replicating synthetic nucleic acids not expressed from vectors or derived by recombinant techniques being subject to the *NIH Guidelines* include:
  - Provide the RAC and OBA with a more complete nucleic acid transfer data base particularly in regard to safety information;
  - Provide maximum degree of safety for research participants;
  - Provide a common public forum for other governmental review bodies, or be advisory to them, and stimulate liaisons between these different review groups; and
  - Enhance scientific expertise by providing scientists greater access to information.

# Discussion Sessions

- Given these potential advantages for inclusion, should all human nucleic acid transfer be consistently covered under the amended *NIH Guidelines* or are there classes of research with certain non-replicating synthetic nucleic acids that should be exempt and why?

# Discussion Questions

- **Several public comments noted that short oligonucleotides differ from other forms of gene transfer in the following:**
  - **Inability to express a transgene;**
  - **Inability to replicate *in vivo*;**
  - **Inability to integrate in cellular genome or modify genomic sequences; and**
  - **Transient duration of action.**

# Discussion Questions

- ❑ **However, biosafety concerns do exist for clinical trials involving synthetic nucleic acids (e.g., off-target gene suppression, saturation of miRNA processing systems, activation of immune responses). Should these biosafety and clinical safety considerations bring this class of nucleic acids under the *NIH Guidelines* for human gene transfer?**

# Discussion Questions

- **If there are 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.) what criteria should be applied to define such classes?**

# Discussion Questions

- ❑ **Would an exception based on function, for example an exemption for non-replicating, synthetic nucleic acids that transiently modify the function of RNA but cannot modify the genome of a cell and do not integrate be reasonable?**

# Discussion Questions

- **If a distinction is to be made between short synthetic oligonucleotides and longer nucleic acid molecules such as expression cassettes or plasmids that may be chemically synthesized, is it possible to identify a size threshold (e.g., 40 nt) for lower risk research that should be exempt?**
  - **Does the size alter the potential function or toxicities?**
  - **Would the same size apply for different types of short oligonucleotides (e.g., siRNA, shRNA, miRNA, antisense, ribozymes, immune stimulators, etc.)?**
  - **Would the use of a number of nucleotides be too arbitrary?**

# Discussion Questions

- ❑ **Should an exception combine a size and functional definition?**

# Discussion Questions

- ❑ Are there certain experiments with short oligonucleotides that should not be exempt because they may result in a long-term effect? For example, induced pluripotent stem (iPS) cells are known to cause teratomas in animal models and human fetal neural stem cells have apparently caused brain tumors to develop in a human subject (Amariglio *et al.*, PLoS Med. 2009, 6(2):e1000029).
- ❑ Though iPS cells are currently reprogrammed using recombinant viral vectors, would the potential future use of synthetic oligonucleotides (e.g. microRNAs, siRNA, antisense nucleic acid etc.) to control the differentiation of stem cells (either induced, embryonic or other) for therapeutic applications in human subjects present sufficient risk to warrant RAC review and public discussion?

