DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Advisory Committee; Notice of Meeting

Pursuant to Pub. L. 92–463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee on March 11–12, 1999. The meeting will be held at the National Institutes of Health, Building 31C, 6th Floor, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892, starting on March 11, 1999, at approximately 9 a.m., and will recess at approximately 5 p.m. The meeting will reconvene on March 12, 1999, at approximately 8:30 a.m. and will adjourn at approximately 5 p.m. The meeting will be open to the public, except for a portion of the day on March 12. In accordance with sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., the meeting may be closed to the public on March 12 from approximately 10:00 a.m. to approximately 10:30 a.m. for the discussion of a protocol. These discussions could disclose trade secrets and commercial property such as patentable material and personal information concerning individuals associated with the protocols, the disclosure of which would constitute a clearly unwarranted invasion of privacy. The meeting will be held to discuss Proposed Actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782, 62 FR 53335, 62 FR 56196, 62 FR 59032, 63 FR 8052, 63 FR 26018) and other matters to be considered by the Committee. The Proposed Actions will follow this notice of meeting. Attendance by the public will be limited to space available.

Debra W. Knorr, Acting Director, Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone (301) 496–9838, FAX (301) 496–9839, will provide summaries of the meeting and a roster of committee members upon request. Individuals who plan to attend and need special assistance, such assign language interpretation or other reasonable accommodations, should contact Ms. Knorr in advance of the meeting. The Office of Recombinant DNA Activities (ORDA) web site is located at *http://www.nih.gov/od/orda* for further information about the office.

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the *Catalog of Federal Domestic Assistance.* Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the *NIH Guidelines.* In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Dated: February 8, 1999.

LaVerne Y. Stringfield,

Committee Management Officer, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Proposed Actions Under the Guidelines

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth proposed actions to be taken under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782, 62 FR 53335, 62 FR 56196, 62 FR 59032, 63 FR 8052, 63 FR 26018). Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee (RAC) at its meeting on March 11–12, 1999. After consideration of these proposals and comments by the RAC, the NIH Director will issue decisions in accordance with the NIH Guidelines.

DATES: Interested parties are invited to submit comments concerning this proposal. Comments received by February 24, 1999, will be reproduced and distributed to the RAC for consideration at its March 11–12, 1999, meeting. After consideration of this proposal and comments by the RAC, the NIH Director will issue decisions in accordance with the NIH Guidelines.

ADDRESSES: Written comments and recommendations should be submitted to Debra Knorr, Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, or by FAX to 301–496–9839.

All comments received in response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX 301–496-9839. The Office of Recombinant DNA Activities' (ORDA) web site is located at *http://www.nih.gov/od/orda* for further information about the office.

SUPPLEMENTARY INFORMATION: The NIH will consider the following actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules:

I. Amendment to Appendix B–I. Risk Group 1 (RG1) Agents

On December 11, 1998, ORDA received a facsimile from Dr. Margarita C. Curras-Collazo, University of California at Riverside, Riverside, California, requesting under Section IV–C–1–(2), Minor Actions, of the NIH Guidelines, to lower the containment level (from Biological Level (BL) 2 to 1) for recombinant adeno-associated vectors (AAV) produced in the absence of helper viruses. Subsequent to this request, ORDA received a telephone call from Ms. Brenda Wong, Biological Safety Officer, University of California at San Diego, La Jolla, California, asking that this determination be reconsidered due to the potential of insertional metagenesis of recombinant AAV. ORDA has solicited the opinion of three experts in the AAV field, in addition to the opinion of the RAC Chair.

It is the opinion of the RAC Chair and the three experts that BL1 is appropriate for recombinant AAV vectors produced

in the absence of helper viruses; therefore, an amendment to the NIH Guidelines is appropriate. Part of the rationale for this decision is based on the fact that experiments involving certain recombinant retroviral vectors, which insert randomly into the genome and could potentially cause insertional mutagenesis, are designated as BL1.

Currently the affected section of the NIH Guidelines states in part: ''RG1 agents are not associated with disease in healthy adult humans. Examples of RG1 agents include asporogenic *Bacillus subtilis* or *Bacillus licheniformis* (see Appendix C–IV–A, *Bacillus subtilis* or *Bacillus licheniformis* Host-Vector Systems, Exceptions), *Escherichia coli*-K12 (see Appendix C–II–A, *Escherichia coli*-K12 Host Vector Systems, Exceptions), and adeno-associated virus types 1 through 4.''

At the March 11–12, 1999, meeting, the RAC will consider an amendment to Appendix B–1, of the NIH Guidelines. The new section, Appendix B–1, is proposed to read:

RG1 agents are not associated with disease in healthy adult humans. Examples of RG1 agents include asporogenic *Bacillus subtilis* or *Bacillus licheniformis* (see Appendix C–IV–A, *Bacillus subtilis* or *Bacillus licheniformis* Host-Vector Systems, Exceptions), *Escherichia coli* K–12 (see Appendix C–II–A, *Escherichia coli* K–12 Host Vector Systems, Exceptions), adeno-associated virus types 1 through 4, and recombinant AAV constructs, in which the transgene does not encode either a tumor suppressor or a toxin molecule and are produced in the absence of a helper virus.

II. Addition to Appendix D of the NIH Guidelines Regarding the Introduction of a Gene Coding for Ampicillin Resistance into *Chlamydia trachomatis*/ Dr. Stothard

In a facsimile dated January 27, 1999, Dr. Diane Stothard of Indiana University, Indianapolis, Indiana, is requesting permission to conduct experiments which involve the introduction of a gene coding for ampicillin resistance into *Chlamydia trachomatis*, a Risk Group 2 agent. According to Section III–A–1-a of the NIH Guidelines, experiments that involve the transfer of a drug resistance trait to a microorganism that is not known to acquire the trait naturally shall be reviewed by the RAC. Ampicillin type drugs are one of the few accepted treatments for pregnant women.

At the March 11–12, 1999, meeting, the RAC will consider a proposed addition to Appendix D, of the NIH Guidelines, to allow the introduction of gene coding for ampicillin resistance into *Chlamydia trachomatis*, a Risk Group 2 agent.

III. Discussion Regarding Prenatal Gene Transfer Research

On January 7–8, 1999, the NIH held a Gene Therapy Policy Conference entitled: Prenatal Gene Transfer: Scientific, Medical, and Ethical Issues. This conference was not an endorsement by the NIH of prenatal gene transfer research. Rather, this conference was an initial step in an ongoing process of active public deliberation among scientists, clinicians, families, policy makers, individuals, and groups of concerned citizens to gather expert views and solicit public opinion regarding the substantive public policy issues raised by prenatal gene transfer research. It is anticipated that continued deliberation of this issues will ultimately lead to the development of NIH and FDA policy in this arena. The conference participants concluded, ''At present, there is insufficient preclinical data to support the initiation of clinical trials involving prenatal gene transfer.'' A substantial number of critical scientific, safety, ethical, legal, and social issues must be addressed before clinical trials proceed in this arena. These issues include (but are not limited to): (1) Efficiency of gene transfer to target cells; (2) specificity of delivery to target cells; (3) level, duration, and regulation of gene expression; (4) appropriate disease candidates; (5) fetal immune response to transgene products and/or vectors; (6) emergence of fetal immune tolerance; (7) effects of gene transfer on pre- and post-natal development; (8) possibility of generation and activation of transmissible vector or virus; (9) possibility of initiating oncogenic or degenerative processes; (10) limitations related to the accuracy of disease diagnosis; (11) implications of diagnostic limitations on the design and conduct of clinical trials; (12) elements of optimal clinical trial design and analysis; (13) definition of clinical endpoints for the analysis of clinical outcomes; (14) potential risk to the fetus and acceptable level of risk to the fetus in human experimentation; (15) potential risk to the pregnant woman; (16) inclusion and exclusion criteria for the pregnant woman; (17) inclusion criteria for the fetus; (18) pre- and post-pregnancy monitoring of the pregnant woman; (19) pre- and post-partum monitoring of the fetus/child; (20) detection and assessment of inadvertent germ-line transmission; (21) ethical issues specific to the fetus; (22) ethical issues specific to the pregnant woman; (23) patient recruitment/enrollment processes; (24) informed consent issues; (25) societal issues; and (26) legal issues.

The RAC will continue to deliberate these issues during the March 11–12, 1999, meeting and at its future meetings.

IV. Presentation on Gonadal Biodistribution of Gene Transfer Vectors and the Potential Risk of Inadvertent Germ-line Transmission

Representatives of the Food and Drug Administration (FDA) and other invited speakers will present an overview of preclinical data related to gonadal biodistribution of gene transfer vectors and the attendant ethical and safety issues related to preclinical assessment of vector biodistribution and potential risk of inadvertent germ-line transmission to the RAC during the March 11–12, 1999, meeting. This discussion serves as a follow-up to the December 15, 1997, and March 9, 1998, discussions between the FDA and the RAC at which FDA representatives informed the RAC of several preclinical studies demonstrating that DNA homologous to gene transfer vectors has been found in gonadal tissue subsequent to vector administration to extra gonadal sites.

On December 15, 1997, Drs. Steven Bauer and Anne Pilaro, Center for Biologics Evaluation and Research, FDA, presented an overview related to the FDA's observation that preclinical animal studies designed to assess vector biodistribution have demonstrated unexpected persistence of vector nucleic acid sequences in gonadal tissue. Specifically: (1) Nucleic acid persistence in gonadal tissues is evidenced by positive polymerase chain reaction (PCR) signals in DNA extracted from whole gonads, and (2) evidence of nucleic acid persistence in gonadal tissues has been observed with multiple classes of vectors, formulations, and routes of administration. The FDA became aware of these data as part of its review of Investigational New Drug (IND) applications.

Representatives of the FDA noted that the following issues must be resolved before the implications of these observations can be determined: (1) The source of the gonadal PCR signal has not been determined, i.e., germ cells, blood cells, or stroma. Current PCR methods for detecting vector sequences are highly sensitive (capable of detecting one vector copy per microgram of cellular DNA); however, there is a high incidence of false positives and negatives. (2) There are limited data about whether these vector sequences are episomal or integrated. (3) It is unknown whether the presence of

vector nucleic acid sequences in gonadal tissue is associated with any developmental effects. FDA representatives welcomed the opportunity to present this information to the RAC and the public as a timely and appropriate mechanism for increasing public awareness of these findings and to stimulate continued public discussion of the implications of these observations.

Under the limits of confidentiality, the FDA could not discuss further specifics of the observations; therefore, the RAC recommended that ORDA should send a letter to all principal investigators of clinical gene therapy trials and all IBCs requesting submission of all available data related to persistence of nucleic acid vectors in gonadal tissue. The RAC requested this information as part of its role and responsibility to ensure public awareness of recombinant DNA issues within the context of the NIH Guidelines. The NIH Guidelines are applicable to all research that is conducted at, or sponsored by, an institution that receives any support for recombinant DNA research from the NIH. ORDA received approximately 80 responses to this request.

During its March 9, 1998, meeting, the RAC discussed these responses. Four responses indicated that vector sequences were detected in either the ovaries or testes in preclinical animal studies; however, the number of responses received was not representative of the number of clinical trials currently registered with ORDA. RAC members expressed concern about the quantity and quality of responses to the ORDA letter. These concerns included whether the information collected thus far was subject to quality control and if researchers took any precautions to prevent contamination of the analyzed tissue. Of additional concern was the fact that many clinical investigators were not conducting appropriate assays to determine the presence of nucleic acid vectors in gonadal tissue.

Based on the limited information available to the RAC at that time, the committee acknowledged its responsibility to raise a cautionary note regarding the possibility that such evidence suggests inadvertent germ-line alteration. The RAC discussed the complexities involved in designing appropriate testing procedures. The RAC concluded that there is a need to initiate well-designed studies to adequately evaluate the implications of finding vector sequences in gonadal tissue.

V. Discussion on Gene Transfer Vector Containment

The NIH Office of Recombinant DNA Activities (ORDA) has received numerous inquiries from research investigators and Institutional Biosafety Committee (IBC) representatives regarding the appropriate containment practices and procedures for the generation and use of multiple classes of gene transfer vectors. During the March 11–12, 1999, meeting, the RAC will initiate a discussion regarding a reexamination of the proper containment level for a wide variety of vectors employed in gene transfer research. In addition, several new methodologies, such as the use of chimeric nucleic acids, that are currently not covered by the NIH Guidelines will be addressed to aid in laying the groundwork for a redefinition of the term ''recombinant DNA.'' The RAC will discuss the need to update the NIH Guidelines regarding appropriate containment practices and procedures for gene transfer vectors in a variety of settings, i.e., laboratories, animals, and human subjects.

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: February 3, 1999.

Lana Skirboll,

Associate Director for Science Policy, National Institutes of Health.

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