RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

September 21, 2005

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

CONTENTS

[Note: The latest Human Gene Transfer Protocol List can be found at the Office of Biotechnology Activities' Web site at <www4.od.nih.gov/oba/rac/protocol.pdf>.]

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]

September 21, 2005

The Recombinant DNA Advisory Committee (RAC) was convened for its 101st meeting at 8:00 a.m. on September 21, 2005, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Diane Wara (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:00 a.m. until 11:30 a.m. on September 21. The following individuals were present for all or part of the meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania Medical Center
Stephen Dewhurst, University of Rochester Medical Center
Howard J. Federoff, University of Rochester
Helen Heslop, Baylor College of Medicine
Terry Kwan, TK Associates
Nicholas Muzyczka, University of Florida
Glen R. Nemerow, The Scripps Research Institute
Steven Piantadosi, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Madison Powers, Georgetown University
Naomi Rosenberg, Tufts University
Diane W. Wara, University of California, San Francisco

Non-voting *Ad Hoc* Members
(Members who have been named to the RAC but whose appointments are pending completion of the conflict of interest screening process)

Robyn S. Shapiro, Gardner Carton & Douglas
Nikunj V. Somia, University of Minnesota, Twin Cities
Luis P. Villarreal, University of California, Irvine

Office of Biotechnology Activities (OBA) Director/Acting RAC Executive Secretary

Amy P. Patterson, Office of the Director (OD), National Institutes of Health (NIH)

***Ad Hoc* Reviewers/Speakers**

Natasha Caplen, National Cancer Institute (NCI), NIH
Carolyn A. Wilson, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA), U.S. Department of Health and Human Services (DHHS)

Nonvoting Agency Representatives

Kristina C. Borror, Office for Human Research Protections, DHHS
Stephanie L. Simek, FDA

NIH Staff Members

[1] The Recombinant DNA Advisory Committee is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Biotechnology Activities should be consulted for NIH policy on specific issues.

Kelly Fennington, OD
Linda Gargiulo, OD
Robert Jambou, OD
Laurie Lewallen, OD
Maureen Montgomery, OD
Marina O'Reilly, OD
Gene Rosenthal, OD
Thomas Shih, OD
Allan Shipp, OD
Gisele White, OD

Others

There were 52 attendees at this 1-day RAC meeting. Attachment I contains lists of RAC members, *ad hoc* reviewers and speakers, and nonvoting agency and liaison representatives. Attachment II contains a list of public attendees.

I. Call to Order and Opening Remarks/Dr. Wara

Dr. Wara, RAC Chair, called the meeting to order at 8:00 a.m. on September 21, 2005. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on August 16, 2005 (70 FR 48167). Issues discussed by the RAC at this meeting included public review and discussion of one protocol, a gene transfer safety assessment board report, a presentation regarding RNAi and its potential application as a therapeutic strategy, and a presentation regarding the FDA draft guidance on observing clinical trial participants for delayed adverse events.

II. Introduction of New RAC Members/Dr. Patterson

Dr. Patterson asked the five members who would be joining the RAC to introduce themselves:

- Dr. Federoff, University of Rochester, is clinically trained in endocrinology and internal medicine and has been conducting experimental neurology research with particular interest in neurologic diseases.

- Dr. Piantadosi, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, is a clinical trials methodologist/biostatistician.

- Ms. Shapiro, Gardner Carton & Douglas, practices health law and is a professor of bioethics and director of the Center for the Study of Bioethics at the Medical College of Wisconsin.

- Dr. Somia, University of Minnesota, Twin Cities, has expertise in apoptosis and in the human immunodeficiency virus (HIV) and HIV vectors.

- Dr. Villarreal, University of California, Irvine, is director of the Center for Bioissues Research.

Dr. Patterson reminded all RAC members of the rules of conduct that apply to them as special Federal Government employees.

III. Minutes of the June 15-16, 2005, RAC Meeting/Drs. Albelda and Nemerow

Dr. Albelda noted that the June 2005 RAC minutes were accurate and complete.

A. Committee Motion 1

It was moved by Dr. Heslop and seconded by Ms. Kwan that the RAC approve the June 15-16, 2005, RAC meeting minutes. The vote was 11 in favor, 0 opposed, and 0 abstentions.

IV. Gene Transfer Safety Assessment Board Report/Drs. Albelda, Heslop, and Wara

Dr. Heslop reported that 122 protocol amendments had been filed in the past 3 months, of which 40 were new reports and 5 were responses to the *NIH Guidelines, Appendix M(1)C(1)*. Although none warranted public discussion, two of the responses to *Appendix M(1)C(1)* were highlighted: (1) administrative responses for protocol #0501-689, A Phase I, Open-Label Study of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN] to Assess the Safety and Tolerability of Intrastriatal Delivery to Subjects with Idiopathic Parkinson's Disease, and (2) responses to and direct comments related to Protocol #0502-699, A Pilot Study of Temozolomide and O^6-Benzylguanine for Treatment of High-Grade Glioma, using Autologous Peripheral Blood Stem Cells Genetically Modified for Chemoprotection.

Dr. Heslop also offered some comments about long-term followup. Three growth factor trials—Protocols #0101-452, #0301-567, and #0309-604—were allowed to reduce the length of the long-term followup period after discussion with the FDA. Three older trials are still providing useful long-term followup data: Protocol #9902-291 targeting the Fanconi's anemia group A gene, Protocol #0001-381 targeting Canavan's disease, and Protocol #0104-465, an alpha-1-antitrypsin (AAT) study in AAT-deficient adults.

Dr. Albelda reported that there had been 13 protocol submissions since June 2005, one of which was selected for public discussion. The OBA staff reviewed the adverse events (AEs) reported. Although none were deemed necessary for public discussion, 18 were A events, 11 of which were new and 7 of which were followup AEs.

V. Interfering Ribonucleic Acid (RNAi) and Its Potential Application as a Therapeutic Strategy

Speaker: Natasha Caplen, Ph.D., NCI, NIH

Dr. Caplen provided an overview of RNA interference and its functional applications. RNAi is an endogenous mechanism involving double stranded RNA (dsRNA) that controls gene expression by silencing. The biological roles of RNAi include control of endogenous gene expression from protein encoding mRNAs, heterochromatin formation, silencing of "selfish" genetic material, and anti-viral responses. RNAi induced down-regulation of expression can occur at the level of RNA, DNA, or protein as determined by the characteristics of the dsRNA trigger, the proteins incorporated into the RNAi mediating RNA-protein complex, and the interaction of the small interfering RNA (siRNA) and the target sequence. At the RNA level, the mechanism of RNAi involves an RNase III enzyme named Dicer, which converts the longer dsRNA into siRNAs of ~ 22 nt. The siRNAs are incorporated into the RNA induced silencing complex (RISC), which specifically cleaves mRNAs with sequence homologous to the siRNA.

RNAi is being exploited through the use of exogenous RNA effectors, primarily synthetic double stranded siRNAS, and short hairpin RNAs (shRNA). The applications of RNAi include functional genomic analysis, drug:target characterization, novel cellular model systems, and therapeutic uses. In 2002, the first potential therapeutic application of RNAi was published in which *ras* expression was down-regulated in a mouse model, suppressing tumorigenicity. RNAi has also been applied to models of dominant negative genetic diseases, such as spinal cerebellar ataxia. A number of studies have demonstrated the use of RNAi to down regulate the expression of the receptor used during infection by HIV-1.

Dr. Caplen described some of the issues to be considered as RNAi moves into the clinic. The effects of using exogenous siRNAs on the normal cellular roles of RNAi need to be considered. To determine if the cellular machinery can be saturated, studies are being conducted using multiple shRNAs, transcriptional and proteomic analyses, miRNA profiling, and functional analysis of the cell. Effects on non-targeted

RNAS are also being studied by microarray expression profiling, bioinformatics, and functional analyses. Another consideration is the potential to activate non-specific dsRNA responses. Mammalian cells respond to dsRNA as part of an antiviral response which frequently results in non-specific decrease in protein translation and cell death. The size of the double-stranded RNA domain and the concentration of that effector may play a significant role in activation. Regarding establishing resistance through mutation, many studies have shown that single-nucleotide changes at specific points in any RNAi effector can completely eliminate RNAi. There could be selective pressure against any shRNA or sRNA introduced into cells, which could lead to resistance as a result of the mutational rate through single-nucleotide changes.

RNAi has proved to be a potent mediator of gene silencing as an endogenous mechanism, although there remains much to understand. RNAi has been successfully exploited as a functional genomics tool in a broad range of species. A move to clinical application will be determined by the ability to assess realistically the implications of any effects on the RNAi machinery and its critical role in normal cellular processes, any effects on other cellular transcripts, and a minimization of nonspecific effects.

VI. Discussion of Human Gene Transfer Protocol #0508-725: A Phase I Pilot Study of Safety and Feasibility of Stem Cell Therapy for Acquired Immune Deficiency Syndrome (AIDS) Lymphoma Using Stem Cells Treated with a Lentivirus Vector Encoding Multiple Anti-HIV RNAs

Principal Investigator:	Amrita Krishnan, M.D., City of Hope National Medical Center
Additional Presenters:	Linda Couto, Ph.D., Benitec, Ltd.; Larry Couture, Ph.D., Beckman Research Institute of City of Hope National Medical Center; John J. Rossi, Ph.D., City of Hope National Medical Center; John A. Zaia, M.D., City of Hope National Medical Center
RAC Reviewers:	Drs. Powers, Rosenberg, and Wara
Ad Hoc Reviewer:	Natasha Caplen, Ph.D., NCI

A. Protocol Summary

The phase I pilot protocol will study the safety and feasibility of gene transfer of RNA-based anti-HIV therapy expressed in lentivirus-transduced hematopoeitic progenitor cells (HPC) in AIDS patients undergoing autologous stem cell transplantation (HCT) for poor prognosis AIDS lymphoma (ARL). The self-inactivated HIV-derived vector, rHIV7-shI-TAR-CCR5RZ, encodes three genes that, when processed in the cell, will make RNA of three types known to inhibit HIV: (1) an RNAi in the form of a short hairpin RNA (shRNA) targeted to an overlapping exon in HIV-1 *tat* and *rev*; (2) an RNA decoy for the Tat-reactive element (TAR) that competes with an HIV protein necessary to make new copies of HIV; and (3) a ribozyme (CCR5RZ) that targets the host cell CCR5 cytokine receptor used by HIV during infection.

Individuals with ARL, who agree to participate in the study, will have a portion of peripheral HPC collected and frozen during the course of standard lymphoma chemotherapy. A portion of these cells will be genetically modified using the rHIV7-shI-TAR-CCR5RZ vector, and an equal portion of cells will remain otherwise unmanipulated to provide the cells needed for standard-of-care HCT. Then, at the time of HCT, the genetically modified stem cells will be infused first, followed the next day by the unmanipulated cells. Participants will be followed for engraftment of the transplanted cells, for adverse events, evidence of RNA expression and DNA marking by the transgene in the peripheral cells over time, and transgene integration site analyses. The HIV-1 infection status will be monitored with routine tests of HIV-1 plasma RNA and CD4 counts, and detectible endogenous HIV-1 RNA will be evaluated for evidence of recombination events with the transgene sequences. The results of the study will help answer the question of whether this new strategy of gene transfer deserves further evaluation as an eventual method of HIV control.

B. Written Reviews by RAC Members

Eight RAC members voted for in-depth review and public discussion of this protocol. Key issues included the first use of a lentiviral vector for gene transfer into hematopoietic progenitor cells in participants who will receive prior myeloablative treatment, first human gene transfer protocol using an RNAi strategy for replication inhibition of HIV in HIV-infected individuals, and the need for analyzing the effect of this protocol on the nature, timing, and discomforts associated with a participant's terminal condition.

Dr. Powers described this protocol as complex and novel and noted that the otherwise admirably complete and cautiously worded informed consent document contains overly technical language. Despite the likelihood that the potential participant population is likely to be somewhat sophisticated regarding treatment options and the nature of the relevant medical conditions, he requested that the more technical language be simplified.

Dr. Rosenberg expressed concern about the possible effects that expression of the vector RNAs may have on the normal function of the transduced cells and requested a discussion of data showing that transduced cells retained function and that the duration of engraftment was similar to that of cells that have not been transduced. She requested a review of the information indicating that expression of all three RNAs improves the anti-HIV response and that expression of the interfering RNA and the ribozyme do not interfere with normal function of hematopoietic stem cells or their differentiated progeny. She also requested a review of data on the effect of the vector on the emergence of drug-resistant mutants.

Dr. Wara requested presentation of the preclinical *in vitro* and nude mouse data supporting the proposed strategy using three forms of anti-HIV RNA, and data regarding the risk of vector recombination with wild-type HIV in such a way that HIV pathogenicity might be increased. She also requested a summary of the data supporting the safety of use of a lentivirus vector into autologous stem cells for transplantation to participants with underlying immunodeficiency. She asked whether safety would be increased by limiting participation to individuals with better controlled HIV (i.e., participants with a viral load < 10,000 copies and a CD4 count > 200). She suggested that optimizing the anti-HIV regimen of the participants to maximally reduce viral load prior to transplantation may decrease the risk of resistance following transgene receipt. Noting that the informed consent document is well written and does not overstate potential benefit to the individual participant, she suggested that the document would be improved by more clearly separating the risks inherent in the proposed myeloablation and the transplantation procedure participants would otherwise receive from the potential risks of the proposed gene transfer. Dr. Wara also requested inclusion of language regarding the timing of pregnancy tests, the requirement for use of an anovulatory agent by all women participants, the requirement for antifungal and *Pneumocystis carinii* pneumonia prophylaxis, and the possibility of intravenous immunoglobulin infusions.

With respect to considering the use of a particular shRNA for the first time in a clinical setting, Dr. Caplen offered three key questions in her review of this protocol:

- Will exogenous shRNA expression affect the cellular role of the RNAi machinery? She requested that a discussion be initiated to determine whether the preclinical data are sufficient to answer this question.

- Will the shRNA interact with another transcript in such a way as to induce an "off-target" effect? Dr. Caplen suggested that the investigators consider the use of bioinformatics analysis, gene expression studies, and/or other assays to assess the likelihood of an off-target interaction between the processed shRNA in rHIV1-shI-TAR-CCR5RZ and a cellular transcript and how to monitor for such an interaction in a clinical setting.

- Will the shRNA or other RNA elements within the vector trigger a global double-stranded RNA response, which would normally result in cell death? She requested that a discussion be initiated to consider whether cell culture experimentation is sufficient or whether suitable *in vivo* experimentation also should be considered.

In addition, Dr. Caplen suggested modifying the informed consent document to make individuals enrolled in this trial clearly aware that exploitation of the RNAi mechanism in this way is a new approach and that this is a developing field of study.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

- Dr. Somia asked about the inclusion of the woodchuck hepatitis virus post-transcriptional regulatory element (WPRE) in the vector.

- Dr. Somia asked about the assay the investigators plan to use to detect replication-competent lentivirus (RCL), postinfusion at 3, 6, and 12 months since the participants are infected with HIV.

- Dr. Dewhurst asked whether individuals with virus that may be resistant to the anti-RNAs, such as those infected with X4 viruses or viruses divergent at the shRNA target, should be included in the trial. He expressed concern that the use of CCR5 blockers may lead to selection of X4 virus in co-infected individuals and X4 viruses may be more pathogenic

- Dr. Piantadosi provided some suggestions for improving study design. He suggested that this trial is a translational trial, rather than a Phase I pilot safety and feasibility study because it is small, tests emerging therapeutic concepts from the laboratory, and it depends fundamentally on a measured biological outcome. The study design of the protocol would benefit from a clear articulation of the essential biological question, explicit definition of failure, and consideration of possible study outcomes which would inform subsequent research.

- Dr. Wara asked the investigators to address the biosafety and public health precautions they propose, because they will be working with lentivirus in HIV-infected individuals.

- Ms. Kwan requested simplification of the language in the informed consent document. In addition to the standard informed consent document for the lymphoma treatment, she recommended a separate document to address the gene transfer.

D. Investigator Response

Drs. Zaia and Rossi responded to RAC questions and concerns in the written reviews and during the meeting with the following information:

- To address the effect of shRNA on the cellular function of the RNAi machinery, a vector was generated that expressed three different shRNAs in CD34+ or T cells and miRNA profiles were assayed by microarray. Changes were observed in only three of 280 miRNAs analyzed, suggesting little impact on the miRNA population.

- Regarding off-target effects, no defects in the differentiation of CD34+ cells expressing the three anti-HIV RNAs were detected by FACS analyses of expected cellular markers. In a hu-SCID mouse model with a human fetal thymus/liver implantation, normal lineage differentiation and macrophage function were observed. For the clinical trial, off target effects will be monitored by FACS analysis of transduced hematopoeitic cells.

- Expression of the shRNA did not appear to induce a global response as measured in CD34+ derived monocytes by levels of interferon alpha or beta, cytokines, chemokines or expression of interferon induced genes. No abnormalities were observed in a fetal rhesus monkey model injected with vector.

- The induction of resistant virus has been observed with vectors expressing a single shRNA; however, the mutated virus was less fit than the parental virus. No resistant virus was detected with the vector expressing the three anti-viral RNAs over a similar 42 day challenge in cell culture. Subjects will be monitored for resistant virus in the clinical trial.

- Regarding inclusion/exclusion criteria based on viral load or CD4 cell counts, the investigators considered the ability to mobilize sufficient progenitor cells the important criterion.

- The WPRE is included in the vector because it aids in the packaging step, but because only pathway promoters will be used, no read-through into the WPRE is anticipated.

- Rather than an RCL assay, a recombination assay will be used to detect the presence of vector sequences in participants' HIV during the 3-, 6-, and 12-month followup periods.

- In addressing the proposed biosafety and public health precautions, the investigators explained that participants will be housed in a high-efficiency particulate air (HEPA)-filtered room that meets all universal precautions normally used for patients undergoing transplantation. The institution also has a biosafety official who oversees the interactions of reagents produced in a biosafety level (BSL) 3 laboratory; the reagent proposed for this protocol is produced in a laboratory that is similar to a BSL-3 laboratory. After bone marrow transplant, participants will be protected from contact with others primarily through the airflow system in the hospital—an operating room HEPA airflow in the rooms and in the corridors outside. When participants go outside, they will wear masks to protect themselves from hospital patients, so there is no major concern that these research participants would spread infection.

E. Public Comment

Dr. Borror commented on the informed consent document's use of the term "gene therapy," which should be changed to "gene transfer." She also noted that the alternative treatment section contained typographical errors that changed the meaning of important phrases, particularly in section 2.

F. Synopsis of RAC Discussion and RAC Recommendations

Dr. Wara summarized the following RAC comments and recommendations:

Scientific/medical/study design issues:

- Additional studies, using microarray and/or bioinformatics analysis, would be useful in assessing the likelihood of an off-target effect between the processed shRNA expressed by rHIV1-sh1-TAR-CC5Rz and cellular transcripts.

- To determine the possible effects that the expression of vector RNAs may have on the function of transduced stem cells, it would be useful to study the differentiation and function of cells in other hematopoietic lineages in addition to monocytes and macrophages.

- Two key goals should influence the inclusion/exclusion criteria: (1) enhancing safety and (2) maximizing the meaningfulness of the outcome variables. A more homogeneous cohort of participants would help optimize the interpretability of the outcome data. In particular, consideration should be given to narrowing the inclusion criteria by:

    - Limiting enrollment to participants with viral loads of less than 10,000 genome copies per milliliter and CD4 cell counts greater than 200

  - Excluding participants infected with both X4 and R5 HIV-1 strains, since the use of an R5 blocker (CCR5RZ) may lead to an increase in the levels of X4 viruses, which have been associated with accelerated disease progression

- Recognizing that this study is potentially a landmark translational clinical trial bridging basic science to the clinic, it is especially important that the study be properly designed to inform subsequent scientific decisionmaking. Toward this end, the study design would be improved by:

  - A clearer articulation of the essential biological question(s) to be addressed

  - An explanation of the statistical rationale for enrolling five participants

  - A clear enumeration of the possible study outcomes and an explanation of how these outcomes will guide subsequent experiments if the underlying scientific hypothesis is confirmed

  - A definition of what constitutes failure in clinical terms, which will help determine whether subsequent follow-on studies should be pursued

Ethical/legal/social issues:

- A clinician who is not involved in the protocol should be engaged to discuss the available options and to provide advice to prospective participants.

- The informed consent document covers both the standard-of-care procedures as well as the investigational gene transfer procedure. To enhance understanding, the informed consent for the experimental component should be presented in a separate document. In addition, to avoid misunderstanding about the potential benefits of the study, the term “gene transfer” should be used instead of “gene therapy.”

- The informed consent document should provide specific recommendations for birth control that include both anovulatory and barrier methods.

- The reading level of the informed consent document is too high and should be simplified to increase comprehensibility.

G. Committee Motion 2

It was moved by Ms. Kwan and seconded by Dr. Powers that the above recommendations be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 11 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VII. A User’s Guide to the FDA’s Draft Guidance: Gene Transfer Clinical Trials—Observing Participants for Delayed Adverse Events

Speaker: Carolyn A. Wilson, Ph.D., FDA

Dr. Wilson presented background and information about the FDA’s draft guidance regarding follow-up of participants in clinical trials. She reviewed the history of the development of the guidance beginning in 1993 through to the document issued in August.

The guidance focuses on two main properties that have the potential to cause delayed events: (1) the persistence of vector sequences due to integration or the potential for latency with subsequent reactivation and (2) transgene-specific effects. Long term risks of persistence of vector sequences will be influenced by the mechanism of persistence (e.g., vector integration with risk of insertional mutagenesis), latency and potential for reactivation (e.g., reactivation of herpesvirus) and the immune status of the

subject. Transgene effects of concern include the potential of the transgene to induce tumorigenesis or autoimmune disease. Also constitutive expression of a regulated gene or ectopic expression may also cause long term effects.

The guidance document provides information about conducting preclinical studies to determine persistence. Biodistribution studies should be conducted which include multiple time points. Persistence is defined as detection of vector throughout all time points in study without any downward trend. Studies should be performed if information about particular vector's persistence is not available. Researchers who have no information about their particular vector with respect to its potential for integration or latency and who cannot perform these studies in preclinical models should perform long-term observations. For most of the commonly used vectors, there are preclinical and clinical data regarding propensity to integrate. Dr. Wilson reviewed the commonly used vector types. Plasmids, poxvirus, adenovirus, and AAV vectors are not considered to have a propensity to integrate, thus, do not require long-term follow-up. Retroviral vectors do require long-term follow-up due to integration as do herpesvirus vectors due to latency with potential for reactivation. Exceptions to be considered include vectors with potential for long-term toxicity based on preclinical studies (e.g., transgene effects), or vectors that have been modified to alter integration potential.

Also included in the FDA's guidance document is an explanation of special considerations to be employed when using retroviral vectors; this explanation represents written guidance for what has been *de facto* practice since January 2003 in response to the results of the clinical trials for individuals with X-linked severe combined immunodeficiency disease. These recommendations apply when retroviral vectors are used to transduce target cells with high replicative capacity and long survival, for example, hematopoietic stem cells. If a surrogate is accessible for assays, the FDA recommends that researchers test for vector sequences every 6 months for the first 5 years and yearly for the next 10 years. This assay may be discontinued in particular individuals if no vector is detected. If vector is detected in >1% of surrogate cells, an assay should be developed to assess the pattern of integration sites. If an oligoclonal or monoclonal pattern develops, integration sites should be determined and subjects should be monitored for signs of malignancy. The document also includes information about key points to include in the informed consent document to accurately reflect the risk of cancer.

The duration of followup is generally recommended as 5 years and is based on the duration of *in vivo* vector persistence, the duration of *in vivo* transgene expression, the exposure of the study population to the vector used in the clinical trial, expected survival rates, and other relevant factors. One exception to the requirement for long-term followup would be if clinical considerations determine that long-term followup studies would have no scientific value due to short life expectancy, multiple morbidities, and/or exposure to other agents. The elements for observation in the first five years include case histories, detection of gene transfer related events, annual visits to healthcare provider, and recording of new malignancies, or neurological, rheumatological, hematological, or autoimmune disorders. From 6-15 years, subjects should be contacted annually and screened if indicated.

Dr. Wilson reminded RAC members that the National Center for Research Resources (NCRR), NIH, provides assistance to academic studies in the form of supporting participants' visits to and routine laboratory tests at the General Clinical Research Centers (GCRCs), providing blood sample storage through the National Gene Vector Laboratories at no cost to NIH-funded studies, and free clonality analyses.

A. RAC Discussion

Questions and comments from RAC members and others included the following:

- Dr. Dewhurst expressed concern about the confusion regarding whether and how these regulations apply. Dr. Simek responded that these regulations apply only to products within the purview of the FDA's Office of Cellular, Tissue, and Gene Therapies (OCTGT). Currently, the FDA's Office of Vaccines Research and Review (OVRR) requests follow-up from particular sponsors.

- Dr. Dewhurst suggested that, once the guidelines are finalized, the FDA notify the institutional biosafety committees (IBCs) nationally about this guidance. The IBCs may find the guidance helpful in evaluating whether a sponsor is supposed to be providing long-term followup.

- Dr. Wara noted that Dr. Patterson offered the OBA to take on the responsibility of notifying the IBCs.

- Dr. Wara wondered whether, with regard to the NCRR's offer to pay for and sponsor the long-term followup, the GCRCs will support the routine laboratory tests needed by most research participants. Dr. Wilson stated that routine laboratory tests would be covered by the GCRCs and that the entire list of covered services is available within the document on the FDA Web site.

- In response to Ms. Shapiro's question as to whether the document addresses a participant's right not to comply with long-term followup, Dr. Wilson responded that the FDA is aware of this issue and therefore believes it should be incorporated as part of the informed consent process at the outset of each protocol to enhance awareness and encourage participation. Some sponsors that are compliant with long-term followup have difficulty in tracking participants over time, and in some cases, sponsors cannot continue their long-term followup plan because participants choose to withdraw from follow-up. The FDA acknowledges that that is a participant's legal right.

- Because it would be helpful in reviewing future protocols, Dr. Wara suggested that the finalized document be placed on the OBA Web site. Dr. Simek noted that the document will be placed on the CBER Web site and suggested that the OBA announce its existence and provide a link to the CBER Web site.

B. Public Comment

Daniel Rosenblum, M.D., FDA, the clinical reviewer who participated in drafting this document, clarified that it is the sponsor's responsibility to examine the product and inform the FDA of the arguments in favor of or against conducting a long-term followup study. The FDA will review the information and either concur or not concur, depending on information that the FDA may or may not be able to share publicly. The informed consent document should note the expectation that participants will be followed for 15 years, including 5 years of close observation, in order to encourage participants to provide that information.

VIII. Closing Remarks and Adjournment/Dr. Wara

Dr. Wara thanked the participants and adjourned the meeting at 11:30 a.m. on September 21, 2005.

[Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, actions are not considered final until approved by the NIH Director.]

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Amy P. Patterson, M.D.
Acting RAC Executive Secretary/OBA Director

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

These minutes will be formally considered by the RAC at a subsequent meeting; any corrections or notations will be incorporated in the minutes after that meeting.

Date: _____

_____

Diane W. Wara, M.D.
Chair

Attachment I
Recombinant DNA Advisory Committee Roster

Chair

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Attachment III
Abbreviations and Acronyms

AAT	alpha-1-antitrypsin
AAV	adeno-associated virus
AE	adverse event
AIDS	acquired immune deficiency syndrome
BRMAC	Biological Response Modifiers Advisory Committee
BSL	biosafety level
CBER	Center for Biologics Evaluation and Research
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
GCRCs	General Clinical Research Centers
HCT	hematopoietic cell transplantation
HEPA	high-efficiency particulate air
HIV	human immunodeficiency virus
IBC	institutional biosafety committee
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	NIH Office of Biotechnology Activities
OCTGT	Office of Cellular, Tissue, and Gene Therapies
OD	Office of the Director, NIH
OVRR	Office of Vaccines Research and Review
RAC	Recombinant DNA Advisory Committee
RCL	replication-competent lentivirus
RCR	replication-competent retrovirus
RNAi	interfering ribonucleic acid
rHIV7-shI-TAR-CCR5RZ	vector encoding three genes that make RNA of three types known to inhibit HIV
shRNA	short hairpin RNA
sRNA	synthetic RNA
WPRE	woodchuck hepatitis virus posttranscriptional regulatory element