RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

January 14, 2008

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]

January 14, 2008

The Recombinant DNA Advisory Committee (RAC) was convened for its 111th meeting at 3:00 p.m. on January 14, 2008, at the National Institutes of Health (NIH), Building 31-C, Conference Room 6, Bethesda, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 3:00 p.m. until 4:30 p.m. on January 14. The following individuals were present for all or part of the January 2008 RAC meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania (*via teleconference*)
Jeffrey S. Bartlett, Columbus Children's Hospital (*via teleconference*)
Stephen Dewhurst, University of Rochester Medical Center (*via teleconference*)
Hildegund C.J. Ertl, The Wistar Institute (*via teleconference*)
Hung Y. Fan, University of California, Irvine (*via teleconference*)
Howard J. Federoff, Georgetown University Medical Center
Jeffrey P. Kahn, University of Minnesota (*via teleconference*)
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation (*via teleconference*)
Prediman K. Shah, Cedars-Sinai Medical Center (*via teleconference*)
Robyn S. Shapiro, Medical College of Wisconsin (*via teleconference*)
Nikunj V. Somia, University of Minnesota, Twin Cities
Scott E. Strome, University of Maryland (*via teleconference*)
Richard G. Vile, Mayo Clinic (*via teleconference*)
David J. Weber, The University of North Carolina at Chapel Hill (*via teleconference*)
David A. Williams, Children's Hospital Boston/Harvard Medical School (*via teleconference*)
John A. Zaia, City of Hope National Medical Center (*via teleconference*)

Office of Biotechnology Activities (OBA)

Jacqueline Corrigan-Curay, Office of the Director (OD), NIH

Nonvoting Agency Representatives

Kristina C. Borror, Office for Human Research Protections, U.S. Department of Health and Human Services (DHHS)
Daniel M. Takefman, Food and Drug Administration (FDA), DHHS

NIH Staff Members

Linda Gargiulo, OD
Bob Jambou, OD
Laurie Lewallen, OD
Maureen Montgomery, OD
Marina O'Reilly, OD
Gene Rosenthal, OD
Tom Shih, OD

[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.

Others

There were 32 attendees at this 1-day RAC meeting.

Attachments

Attachment I contains lists of RAC members and nonvoting agency and liaison representatives. Attachment II contains a participant list. Although this meeting was open to the public, there were no public attendees at this RAC meeting. Attachment III is a list of abbreviations and acronyms used in this document.

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

Dr. Federoff, RAC Chair, called the meeting to order at 3:00 p.m. on January 14, 2008. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* was initially published in the *Federal Register* on December 20, 2007 (72 FR 244). The issue discussed by the RAC at this meeting focused on followup to a serious adverse event (SAE) in a human gene transfer trial using an adeno-associated viral (AAV) vector.

Dr. Corrigan-Curay reminded RAC members of the rules of conduct that apply to them as special Federal Government employees, read into the record the conflict of interest statement, and suggested that questions be addressed to the OBA committee management officer.

II. Followup on a Serious Adverse Event in a Human Gene Transfer Trial (OBA Protocol #0504-705) Using an Adeno-Associated Viral Vector: RAC Conclusions

Presenter: Dr. Corrigan-Curay

Dr. Federoff explained that the purpose of this RAC meeting was to reach consensus on the RAC's assessment, findings, and conclusions regarding this SAE. He noted that there had been robust discussions on this subject and a considerable number of e-mails among RAC members in an effort to find the best way for the RAC to draw its conclusions.

A. Presentation of Draft Statement

Dr. Corrigan-Curay presented a set of 17 slides for discussion by RAC members. Slide topics included the RAC final assessment, specific findings with respect to the role of gene transfer, RAC recommendations on trial design, and RAC recommendations on informed consent. The draft wording presented for discussion read as follows:

RAC Final Assessment

It is the Committee's opinion that this patient's unfortunate death was primarily a result of an opportunistic infection, disseminated histoplasmosis with subsequent bleeding complications, and multiorgan failure. Her apparent risk factor for such an infection was her systemic RA therapy, chiefly the TNF-antagonist drug adalimumab.

The possibility of an immune response to the AAV vector in this patient cannot be evaluated due to lack of data.

Specific Findings with Respect to the Role of Gene Transfer

There was no evidence of contamination of the product.

The evidence does not support the theory that a helper virus led to widespread dissemination of replication-competent AAV.

- The majority of the vector remained in the knee at the injection site with only extremely low levels of the vector present outside the knee.

- The *AAV2rep* gene, which may indicate replication-competent AAV, was found in the right knee as expected. It was also found in very low levels in the heart and trachea. Given the lack of vector in those sites, the detection of *AAV2rep* likely represents a natural infection.

Transgene production does not appear to have played a role in the clinical course.

- There were declining serum levels of tumor necrosis factor (TNF) antagonist in the serum after the subject stopped systemic therapy.

- Levels of TNF antagonist in the serum never exceeded the expected steady state.

The fact that this does not appear to have been a factor in this case does not diminish the importance of having an assay to specifically detect and quantify levels of the transgene product.

Although steady-state serum levels were not above those that had been predicted, the degree of functional TNF inhibition cannot be determined.

The possible role of an immunologic response to the AAV vector in the clinical course cannot definitively be ruled out due to lack of data.

- Whole-blood samples from before and after administration of the product were not available for CD8+ capsid-specific T-cell assays.

- The absence of significant vector in the liver and the elevated anti-AAV titer (1:128) are not sufficient data to exclude an immune response.

There is no clear laboratory evidence that the intra-articular injection of the gene transfer vector contributed to the subject's clinical course or her death.

RAC Recommendations on Trial Design

The RAC recommends that AAV trials monitor for anti-capsid T cells by drawing blood both before and at multiple points after the gene transfer. This may help both in interpretation of adverse events and shed light on the safety of AAV vectors generally.

- The FDA currently recommends such monitoring for AAV trials.

This case further underscores the importance of developing assays to distinguish the gene transfer product from other treatments the subject is receiving.

The potential role of immunosuppression in altering the risks to subjects enrolled in gene transfer trials needs to be carefully considered.

Clinical criteria for the timing of dosing, especially in safety trials, should be thought out in advance and articulated in the protocol. Special attention should be given to:

- Screening for signs of active infection prior to dosing

- Obtaining lab results prior to dosing

To enhance the safety for participants in gene transfer trials, consider developing a medical card that would include the following:

- A brief description of the vector and a Web-based link to find out more information
- 24-hour contact numbers for the study investigators
- A list of samples that should be collected upon admission to a hospital

Protocols should plan for the additional blood and other samples that may need to be collected in event of a serious adverse event and think through the logistics of collection should the subject be under the care of physicians who are not involved with the trial.

The logistics of an autopsy, including a detailed protocol that could be shared with an outside institution, as well as considering mechanisms for transfer of the decedent from an outside institution to the institution conducting the trial should also be developed in advance.

RAC Recommendations for Trial Design: Informed Consent

In early-phase trials it is critical to take steps to actively prevent therapeutic misconception in the informed consent process.

Investigators need to recognize that their own belief in their study may also lead to therapeutic misconception.

In cases where the investigator is also the subject's physician:

- If an adverse event occurs, the investigator may become both the caregiver and investigator at the same time. While it is not known to be the situation in this case, such a situation would present an apparent conflict of commitment. Such a conflict should be anticipated in complex trials such as this and addressed in the protocol.
- The potential conflict of roles should be clearly articulated in the consent.
- The subject should be assured that a decision not to participate in the study would not impact their relationship with their physician.
- Consider having a third party involved in the consent process to insure the subject understands the different, and possibly competing, roles that the investigator/physician will perform.
- Consider providing the opportunity to enlist an independent physician in the event of a medical complication.

A discussion of the importance of an autopsy is critical in clinical trials and it may be prudent to involve the family, if possible, that discussion.

The *NIH Guidance on Informed Consent for Gene Transfer* (http://www4.od.nih.gov/oba/rac/ic/) provides a potential resource for information regarding these difficult consent issues.

B. Summary of RAC Discussion

Led by Dr. Corrigan-Curay and Dr. Federoff, RAC members discussed the meaning and content of each of the paragraphs listed above and suggested a variety of changes to each statement to clarify meaning,

simplify wording, and draw appropriate conclusions from the data presented at the September 2007 and December 2007 RAC meetings. Issues and specific wording were discussed one paragraph at a time, and the RAC reached consensus on each paragraph before proceeding to the next segment of the statement.

Extensive discussion ensued regarding the overall RAC statement and whether without evidence of an immune response to the AAV vector, this should be included on the initial slide which is the final assessment. Some members felt this was already addressed in subsequent slides and to include it upfront gave more weight than was warranted given the lack of data. Members suggested several rewordings such that the emphasis would be placed on her death being attributed primarily to an opportunistic infection. Dr. Federoff summarized this part of the discussion as agreement that the disseminated histoplasmosis and the retroperitoneal bleed were the proximate causes of her demise, as can best be determined. A minority but strong voice among RAC members opined that the absence of a certain type of data makes it difficult to fully evaluate what might have precipitated or contributed to this individual's clinical course; this opinion was incorporated into the wording of the overall statement.

Dr. Strome suggested that the wording be clear and that terms be defined such that statements in this document would not be perceived as pertaining to other gene transfer trials using a different AAV.

Drs. Ertl and Zaia requested rephrasing the discussion of the laboratory evidence to make it clear that none of that laboratory evidence supports the conclusion that the intra-articular injection of the gene transfer vector contributed to the participant's clinical course or her death. This wording leaves open the possibility that additional studies may have yielded data that might possibly have supported that conclusion, but insufficient laboratory samples were collected to perform such studies.

Regarding the specifics to be included on a medical card to be carried by each research participant, discussion ensued about whether the principal investigator of the study or a study clinician should be listed as the contact person. The conclusion of this discussion was that the contact should read "principal investigator or designee" and that it would be up to the investigators to provide 24-hour coverage of a contact telephone number.

Discussion also took place regarding the specifics of which samples should be taken when a research participant receives non-routine care; this discussion grew out of the unfortunate absence of some samples and data that would have assisted in determining the cause of this participant's death. The RAC also discussed how to handle consent to collect these samples.

Several RAC members said they would provide editorial comments to Dr. Corrigan-Curay after this meeting.

C. Public Comment

Public attendees offered no comments.

D. Final RAC Statement

After the above discussion, the following wording was crafted as the RAC's final statement:

> **RAC Final Assessment**
>
> It is the Committee's opinion that this patient's unfortunate death was primarily a result of an opportunistic infection, disseminated histoplasmosis with subsequent bleeding complications, and multiorgan failure. Her apparent risk factor for such an infection was her systemic rheumatoid arthritis therapy, chiefly the TNF-antagonist drug adalimumab. The contribution of an immune response to the AAV vector could not be evaluated.

Specific Findings with Respect to the Role of Gene Transfer

There was no evidence of contamination of the gene transfer product.

The evidence does not support the theory that a helper virus led to widespread dissemination of replication-competent AAV.

- The majority of the vector remained in the knee at the injection site, with only extremely low levels of the vector present outside the knee.

- The *AAV2rep* gene, which may indicate replication-competent AAV was found in the right knee as expected. It was also found in very low levels in the heart and trachea. Given the lack of vector in those sites, the detection of *AAV2rep* likely represents a natural infection.

Transgene product production does not appear to have played a role in the clinical course.

- There were declining blood levels of TNF antagonist in the serum after the subject stopped systemic therapy.

- Levels of TNF antagonist in the blood never exceeded the expected steady state.

Although steady-state blood levels were not above that predicted for a systemically administered TNF antagonist, the degree of functional TNF inhibition due to the transgene product could not be determined.

The fact that systemic levels of the transgene product do not appear to have been a factor in this case does not diminish the importance of having an assay to specifically detect and quantify levels of the transgene product.

The possible role of an immunologic response to the AAV vector in the clinical course cannot definitively be ruled out due to a lack of data.

- Blood samples from before and after administration of the product were not available for CD8+ capsid-specific T-cell assays.

- The absence of significant vector content in the liver and the elevated anti-AAV titer (1:128) are not sufficient data to exclude a cellular immune response.

None of the available laboratory evidence supports the conclusion that the intra-articular injection of the gene transfer vector contributed to the subject's clinical course or her death.

RAC Recommendations on Trial Design

The RAC recommends that AAV trials monitor for anticapsid T cells before and at multiple points after each gene transfer. This may help both interpret adverse events and shed light on the safety of AAV vectors generally.

- The FDA currently recommends such monitoring for AAV trials.

The RAC recommends developing assays to distinguish the gene transfer product from other biological treatments the subject may be receiving.

The potential role of immunosuppression in altering the risks of the gene transfer vehicle and/or gene transfer product should be assessed.

Clinical criteria for deferring administration of the gene transfer vector, especially in safety trials, should be carefully considered in advance and clearly stated in the protocol. Special attention should be given to:

- Screening for signs of active infection prior to dosing
- Obtaining laboratory results prior to dosing

To enhance participant safety in gene transfer trials, the investigators should consider developing a medical card that would include the following:

- A brief description of the vector and a web-based link to find out more information
- 24-hour contact telephone numbers so the study's principal investigators or designee can be contacted
- A detailed list of samples that should be collected when a study subject seeks medical attention for non-routine care

Protocols should include a plan for the additional blood and other samples that may need to be collected in event of an SAE and think through the logistics of collection should the subject be under the care of physicians who are not involved with the trial or the subject is unable to provide consent.

The logistics of an autopsy, including a detailed protocol that could be shared with an outside institution and mechanisms for transfer of the decedent from an outside institution to the institution conducting the trial should also be developed in advance.

RAC Recommendations on Trial Design: Informed Consent

In early-phase trials, it is critical to take steps to actively prevent therapeutic misconception in the informed consent process.

Investigators need to recognize that their own belief in their study also may lead to therapeutic misconception.

In cases where the investigator is also the subject's physician:

- The informed consent document should clearly articulate the potential conflict of roles.
- Subject should be assured that their decision *not* to participate in the study would not impact their relationships with their physicians.
- The investigators should consider involving a third party in the consent process to ensure that subjects understand the different and possibly competing roles, that the investigator/physician will perform.
- The investigators should consider providing the opportunity to enlist an independent physician in the event of a medical complication.

A discussion of the importance of an autopsy is critical in clinical trials, and it may be prudent to involve the family, if possible, in that discussion prior to enrollment.

The *NIH Guidance on Informed Consent for Gene Transfer* (http://www4.od.nih.gov/oba/rac/ic/) provides a resource for information regarding these difficult consent issues.

E. Committee Motion 1

Dr. Kirchhoff moved and Dr. Ertl seconded a motion that the RAC approve this final statement, as revised, regarding the SAE that occurred in Protocol #0504-705. The vote was 12 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Closing Remarks and Adjournment/Dr. Federoff

Dr. Federoff thanked the RAC members and OBA staff and adjourned the meeting at 4:30 p.m. on January 14, 2008.

[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.]

_____
Jacqueline Corrigan-Curay, J.D., M.D.
RAC Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and the following 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 into the Minutes after that meeting.

Date: _____

_____
Howard J. Federoff, M.D., Ph.D.
Chair
Recombinant DNA Advisory Committee

Attachment I
Recombinant DNA Advisory Committee Roster

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Attachment II
Participant

Joseph Kanabrocki, University of Chicago *(via teleconference)*

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
DHHS	U.S. Department of Health and Human Services
FDA	Food and Drug Administration, DHHS
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
RA	rheumatoid arthritis
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
TNF	tumor necrosis factor