
RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 19-21, 2007

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

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[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 Meeting¹**

June 19-21, 2007

The Recombinant DNA Advisory Committee (RAC) was convened for its 108th meeting at 8:00 a.m. on June 19, 2007, at the National Institutes of Health (NIH), Building 31-C, Conference Room 10, Bethesda, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 5:45 p.m. on June 19, from 8:00 a.m. until 6:00 p.m. on June 20, and from 8:30 a.m. until 3:30 p.m. on June 21. Most of the June 19 meeting date was a symposium on adeno-associated virus (AAV) vectors; the summary of that symposium is provided as a separate document. The following individuals were present for all or part of the June 2007 RAC meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania Medical Center
Stephen Dewhurst, University of Rochester Medical Center
Hildegund C.J. Ertl, The Wistar Institute
Howard J. Federoff, Georgetown University Medical Center
Jane Flint, Princeton University
Ellen E. Grant, HealthNow New York Inc.
Helen Heslop, Baylor College of Medicine
Jeffrey P. Kahn, University of Minnesota
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation
Nicholas Muzyczka, University of Florida
Naomi Rosenberg, Tufts University
Robyn S. Shapiro, Medical College of Wisconsin
Nikunj V. Somia, University of Minnesota, Twin Cities
Scott E. Strome, University of Maryland Medical Center
David J. Weber, The University of North Carolina at Chapel Hill
Lee-Jen Wei, Harvard University

Office of Biotechnology Activities (OBA)

Jacqueline Corrigan-Curay, Office of the Director (OD), NIH
Amy P. Patterson, OD, NIH

Ad Hoc Reviewers and Speakers

Andrew Bakker, Amsterdam Molecular Therapeutics
John Bennett, National Institute of Allergy and Infectious Diseases (NIAID), NIH
Otis W. Brawley, Emory University
Toni Cathomen, Charité Medical School, Berlin, Germany (*via teleconference*)
Nicholas Crispe, University of Rochester
David W. Hackstadt, NIAID, NIH (*via teleconference*)
Katherine A. High, The Children's Hospital of Philadelphia
Anthony Maurelli, Uniformed Services University of the Health Sciences
Janneke Meulenberg, Amsterdam Molecular Therapeutics
Claudia Mickelson, Massachusetts Institute of Technology (*via teleconference*)

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.

Ellis Neufeld, Children's Hospital Boston (*via teleconference*)
Paul J. Orchard, University of Minnesota
Marina O'Reilly, OBA, NIH
John R. Papp, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services (DHHS)
R. Jude Samulski, The University of North Carolina at Chapel Hill
Leonard B. Seeff, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH
Susan Wang, CDC (*via teleconference*)
James M. Wilson, University of Pennsylvania
Kimberly Workowski, CDC, DHHS (*via teleconference*)
J. Fraser Wright, The Children's Hospital of Philadelphia

Nonvoting Agency Representatives

Kristina C. Borrer, 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

Valerie Bonham, Office of the General Counsel, OD, NIH
Sandra Bridges, NIAID, NIH
Vijay Camasamudram, National Institute on Deafness and Other Communication Disorders (NIDCD), NIH
Peter Colosi, National Eye Institute (NEI), NIH
Linda Gargiulo, OD, NIH
Mary Groesch, OD, NIH
Kathryn Harris, OD, NIH
Bob Jambou, OD, NIH
Steve Kellstrom, NIDCD, NIH
Laurie Lewallen, OD, NIH
Maureen Montgomery, OD, NIH
Mark Mortin, National Institute of Child Health and Human Development, NIH
Stuart Nightingale, OD, NIH
Michael Pensiero, NIAID, NIH
Sarah Read, NIAID, NIH
Maryann Redford, NEI, NIH
Gene Rosenthal, OD, NIH
Rita Sarkar, National Heart, Lung, and Blood Institute, NIH
Barbara Schuler, National Cancer Institute, NIH
Tom Shih, OD, NIH
Allan Shipp, OD, NIH
Frosso Vougaropoulou, NIAID, NIH
Fei Wang, NEI, NIH
Bruce Whitney, OD, NIH
Yong Zeng, NIDCD, NIH

Others

There were 162 attendees at this 3-day RAC meeting.

Attachments

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. Attachment III is a list of abbreviations and acronyms used in this document.

- There are no preclinical *in vivo* data to support the plan to disrupt the glucocorticoid receptor as a way of preventing attenuation of the T-cell antitumor response in the presence of systemic high-dose steroids. (Research participants receive high doses of steroids to alleviate intracranial pressure from the tumor.) Conducting animal studies to test this assumption would strengthen the protocol.

Clinical/Trial Design Issues

- Positron emission tomography (PET) can detect cells expressing the reporter gene. PET should be used to further refine the protocol.
- Alloclone-002 consists of gene-modified allogeneic cord blood cells. Monitoring for immunologic reactions to Alloclone-002, particularly since it is to be administered four times, is critical for enhancing the safety of this approach.

Ethical/Social/Legal Issues

- The investigators should make the following changes to the informed consent document:
 - It should be written at an eighth-grade reading level. In particular, it is critically important that the suicide gene technology be described in simple, clear, and understandable terms.
 - Alternatives to participation must be included. Alternatives for these patients are limited to palliation and hospice care.

G. Committee Motion 3

Dr. Federoff summarized the RAC recommendations to include a variety of preclinical, clinical, and ethical/social/legal issues, which will be included in the letter to the investigators and the sponsor expressing the comments and concerns of the RAC. No official motion was made or seconded regarding these summarized recommendations. The vote was 15 in favor, 0 opposed, 0 abstentions, and 1 recusal.

IX. Discussion of Human Gene Transfer Protocol #0704-852: A Phase I Open-Label Clinical Trial for the Treatment of β -Thalassemia Major with Autologous CD34+ Hematopoietic Progenitor Cells Transduced with Thalagen™, a Lentiviral Vector Encoding the Normal Human β -Globin Gene

Principal Investigator: Farid Boulad, M.D., Memorial Sloan-Kettering Cancer Center (MSKCC)
Additional Presenters: Christopher Ballas, Ph.D., Errant Gene Therapeutics, LLC; Patricia J. Giardina, M.D., Weill Cornell Medical College; Patrick Girondi, Errant Gene Therapeutics, LLC; Richard J. O'Reilly, M.D., MSKCC; Isabelle Riviere, Ph.D., MSKCC; Michel Sadelain, M.D., Ph.D., MSKCC; John Tisdale, M.D., National Institute of Diabetes and Digestive and Kidney Diseases
Sponsor: Errant Gene Therapeutics, LLC
RAC Reviewers: Drs. Heslop, Kodish, and Rosenberg
Ad hoc Reviewer: Ellis Neufeld, M.D., Ph.D., Children's Hospital Boston (*via teleconference*)

Dr. Albelda recused himself from discussion of this protocol due to a conflict of interest.

A. Protocol Summary

The proposed study is a Phase I clinical trial using globin gene transfer technology for the treatment of β -thalassemia major. The β -thalassemias are congenital blood disorders caused by mutations that affect

the β -globin gene and greatly reduce or abolish hemoglobin synthesis. The resulting red blood cells are short lived and are deficient oxygen carriers. The thalassemia syndrome, which includes severe anemia, can be cured by transplantation of blood-forming stem cells from a healthy donor. However, this option is not available to most patients, for whom a matched, related donor is not available. Most patients must settle for palliative therapy based on lifelong transfusions and iron chelation, a pharmacological treatment that aims to delay the inexorable buildup of iron that accompanies chronic transfusion. Despite considerable progress in the management of transfusion therapy, iron accumulation (which causes cardiac, endocrine, and osteoarticular complications) and infectious complications still cause progressive morbidity in a fraction of patients. Death from cardiomyopathy due to iron overload remains the leading lethal complication of this therapy.

The goal of globin gene transfer is to restore the capacity of the subject's own hematopoietic stem cells to generate red blood cells containing sufficient hemoglobin to achieve transfusion independence. CD34+ hematopoietic cells will be transduced with a lentiviral vector derived from HIV-1 encoding human β -globin. The transfer of a regulated β -globin gene has been shown to correct hemoglobin synthesis in several animal models of β -thalassemia. This approach is not restricted by the availability of a donor, since the subject is also the donor. After genetic modification, the blood-forming cells are returned to the patient without the risks of immune rejection and graft-versus-host disease (GVHD) associated with allogeneic bone marrow transplantation. A "reduced intensity conditioning regimen" based on administering an intermediate dose (8 mg/kg) of busulfan will be used to prepare acceptance of the incoming transduced cells.

This protocol will be offered to subjects 15 years of age and older who lack a matched, related bone marrow transplant donor. The postinfusion monitoring will focus on the safety and tolerability of this experimental treatment as well as the molecular monitoring of the persistence and function of the delivered globin gene. The data generated in this clinical study will be reviewed by an independent drug safety monitoring board at each participating clinical site.

B. Written Reviews by RAC Members

Eight RAC members voted for indepth review and public discussion. Key issues included the following: first application of gene transfer for thalassemia and only the second protocol to use lentiviral vectors for a monogenic disease, safety issues that include the risk of insertional mutagenesis because lentiviral vectors integrate into the genome, and the inclusion of children as young as 15 years of age in the study population, thus adding to the protocol's risk profile and risk-benefit calculation.

Three RAC members and one *ad hoc* reviewer provided written reviews of this proposed Phase I trial.

Dr. Heslop suggested that the investigators readdress the rationale for the inclusion criterion regarding lacking a matched sibling donor, given that more recently published studies with unrelated donor transplant show a survival of 80 percent and a disease-free survival (DFS) rate of 66 percent. She expressed concern that many of the research participants for this proposed trial might have splenomegaly and an expanded marrow, and thus the possibility that the risk of side effects might be higher than in normal donors. Although the investigators state that the transduced cells will be frozen while replication-competent lentivirus (RCL) testing and vector number copy determination studies are performed, Dr. Heslop wondered whether the investigators plan to assay viral integration sites before infusion and whether potential integrations would result in the experimental product not being released. Dr. Heslop suggested five enhancements to the informed consent document, including ensuring that the language is at the eighth-grade level, changing wording that implies therapeutic benefit, adding a request for autopsy, and adding information about how participation in this trial might affect the results of subsequent HIV testing.

Dr. Kodish noted that the informed consent document was clear and well written for the intended audience. He requested additional information about the process of using a patient advocate, especially the proposed approach to assent with participants between 15 and 18 years of age, including whether they will be interviewed without their parent(s) present. Dr. Kodish suggested that terminology in the

informed consent document be changed from “gene therapy” to “gene transfer” to avoid the appearance of therapeutic benefit and that all terminology (e.g., “pulmonary fibrosis”) be defined in lay terms.

Dr. Rosenberg asked about the level of β globin production in differentiated human cells compared to normal production. She asked the investigators to provide an update on the linear amplification-mediated polymerase chain reaction (LAM-PCR) analysis from the primate study, which was said to be in progress, to clarify the possibility of clonal expansion of particular subsets of engrafted cells observed in the various mice tested and whether retroviral integration occurred in any of these animals. Although the risk of RCL appears low, Dr. Rosenberg suggested that the investigators comment on the rationale regarding the birth control recommendation, especially at early points in the study. She also asked for further explication of the rationale for the age of the study participants and which aspects might be compromised if the initial study was limited to adults.

Noting that the science underlying this protocol and the murine models that allowed development of this vector are compelling and well presented, *ad hoc* reviewer Dr. Neufeld stated that the protocol and informed consent document overstated issues in regard to the “palliative” alternative therapy of lifelong hypertransfusion and consequent need for iron chelation therapy. He noted the availability of the oral chelator, deferasirox, particularly for patients with heart disease, the decreased risk of Hepatitis C infection, and the improved survival statistics for patients born after 1982. Although the modest accrual goal of three to five research participants per year is justified based on the small North American thalassemia population and the stringent enrollment criteria, he requested that the investigators comment further on the possibility that three per year might be so slow as to threaten the long-term status of the study if the state of the art evolves over a 3-year time horizon. Dr. Neufeld noted that the entry criteria are somewhat ambiguous regarding the number of transfusions, which could allow enrollment of thalassemia intermedia subjects and be a potential problem for the secondary end point of following required transfusion burden after gene transfer. He stated that the survival statistics for transfusion/chelation are relatively misleading and suggested that the investigators revise this wording in the informed consent document to stress the positive survival experience that has been seen in the most recent trials.

C. RAC Discussion

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

- Dr. Weber suggested changing wording in the informed consent document that implies therapeutic benefit.
- Dr. Ertl wondered about the need for additional preclinical studies to better understand whether there is an enrichment or selection for specific clones when passed from mice to mice.

D. Investigator Response

Regarding the rationale for enrolling participants lacking a matched sibling donor in light of recent data on from transplant from HLA-matched unrelated donors, the investigators reviewed that data and asked whether a mortality of 20 percent, a DFS rate of nearly 70 percent, and a GVHD risk of 18 percent are acceptable in patients with thalassemia major.

The investigators stated that viral integration sites would not be assayed before infusions, since there are no available data to assess the reliability and predictive value of such information. However, genomic DNA will be stored for eventual retrospective analyses. Specific integration sites will not be screened even after integration site analysis unless the integration analysis suggests oligoclonal or monoclonal dominance and/or clinical evidence suggests abnormal cell counts or histology—or as otherwise indicated in the appropriate FDA guidance.

Data from preclinical studies conducted by the investigators indicate that the level of expression of β -globin in human cells is similar to that found in mouse cells; additional ongoing studies aim to confirm

whether similar levels of expression are to be expected in research participants. Taken together, data gathered and from ongoing studies suggest that transduced hematopoietic progenitor cells harboring one or two vector copies should, on average, express β -globin in a therapeutic range.

With regard to their study of TNS9.3 in rhesus macaques, the investigators averred that low-level marking in the animals had so far precluded reliable amplification of integration sites due to competition by internal vector sequences. Analysis of murine integration sites indicated that integration of the globin vector was similar to the expected pattern for lentiviral vectors (i.e., frequent integration within genes, including some oncogenes).

Besides the aspects of the gene transfer, research participants in this proposed study will receive a chemotherapy agent (busulfan) as part of the preparative regimen. For that reason, the investigators included in this protocol a recommendation for the use of birth control.

In response to questions about the age range of potential participants, the investigators explained that their experience with transplanting thalassemia major patients indicates that patients who are 10 to 16 years of age already show extensive iron deposition in the liver as well as evidence of fibrosis. Recent studies have demonstrated that the median age for the onset of severe complications of thalassemia and its treatment is 16 years. Patients between the ages of 15 and 18 years with evidence of early complications most probably will have higher risks of complications with allogeneic transplantation based on organ toxicity, especially if they receive grafts from unrelated donors. In addition, the age of 15 years also was chosen because, by that age, the probability of subsequently having a human leukocyte antigen (HLA)-matched sibling born to the family is radically decreased.

The investigators explained the proposed use of a patient advocate, a process that was discussed with and approved by the chair of their institutional review board (IRB). An experienced senior IRB member will be present at the time of the consent discussion with potential research participants and their families to ensure that the information provided is not biased and that everyone adequately understands the trial, the experimental treatment to be given, the risks associated with this experiment, and the assessments and tests required prior to and following the collection, modification, and administration of stem cells.

Dr. Sadelain explained about additional preclinical studies that are ongoing. In one cohort of approximately 300 mice, the investigators are looking at integration sites and for the presence of enrichment or selection for specific clones. In principle, because the β -globin vector is tissue specific and not expressed in hematopoietic stem cells, there is no expectation that it will promote preferential clonal expansion.

The investigators agree to clarify the protocol and informed consent document regarding Dr. Neufeld's comments about the oral chelator, risks of infection and younger cohort survival.

E. Public Comment

Public attendees offered no comments.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

The following observations and recommendations were made during the RAC's in-depth review and public discussion:

Preclinical Issues

- Insertional mutagenesis is a safety concern for any protocol using a retroviral vector in hematopoietic cells. Although the planned studies of vector integration in mice should yield useful safety data, it is not clear what steps will be taken if clonal expansions due to insertional oncogenesis are seen. Further consideration should be given to this possibility, and a contingency plan should be developed for the protocol.

- Contaminants in the vector, such as adenoviral E1a or SV40 T-antigen transcripts from the packaging cells, could increase the risk of oncogenesis. Screening the vector with a sensitive assay such as reverse transcriptase polymerase chain reaction (RT-PCR) should be considered.

Clinical/Trial Design Issues

- It is not clear what steps will be taken if clonal expansions due to insertional oncogenesis occur at the clinical stage. A contingency plan addressing this possibility is needed.
- Studies are currently under way that will provide data on the safety of administering GCSF in thalassemia patients undergoing transplantation. Since data from the studies will be relevant to this protocol, it would be important to obtain the data as soon as the study is completed.
- Since only patients with thalassemia major are eligible for the protocol, the inclusion criterion related to the blood transfusion requirements needs to be clarified.
- In clinical practice, one of the goals of hypertransfusion in thalassemia is suppression of endogenous erythropoiesis, for example, by keeping the hemoglobin level at 10 g/dL or higher. Transfusion dependency is one of the study end points, but if transfusions are continued in the postgene transfer period using the same hemoglobin threshold, it will be difficult to determine the effect of the gene transfer. The transfusion criterion for the 3- to 5-month period following vector administration should be specified in the protocol and discussed in the informed consent document.
- The protocol overstates the inadequacies of current therapy in two ways. First, the document fails to acknowledge that the disease is well controlled in some patients. Second, the document overstates the risk of infection from blood transfusions. Improvements in screening practices have reduced the risk of transmission of infectious diseases such as hepatitis C, and it is no longer considered a “significant” risk even for patients undergoing multiple transfusions.

Ethical/Social/Legal Issues

- As a safety study, the potential benefits of the protocol are theoretical at best, a point made adequately in the informed consent document. However, the discussion of gene transfer studies that have been successful is misleading and should be deleted.

G. Committee Motion 4

Dr. Federoff summarized preclinical, clinical, and ethical/social/legal issues, which will be included in the letter to the investigators and the sponsor expressing the comments and concerns of the RAC. No official motion was made or seconded regarding these summarized recommendations. The vote was 16 in favor, 0 opposed, 0 abstentions, and 1 recusal.

X. Consideration of Proposed Major Action: Under Section III-A-1 of the *NIH Guidelines: Tetracycline Resistance and *Chlamydia trachomatis**

Principal Investigator: Daniel Rockey, Ph.D., Oregon State University
Additional Investigator: Walter E. Stamm, M.D., University of Washington (UW) School of Medicine
RAC Moderator: Dr. Kirchhoff

A. Presentations