RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 18 and 19, 2003

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]

June 18-19, 2003

The National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) was convened for its 91st meeting at 8:30 a.m. on June 18, 2003, at the Bethesda Marriott Hotel, Rockville Pike, Bethesda, MD. Dr. Theodore Friedmann (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 5:15 p.m. on June 18 and from 8:30 a.m. until 12:00 noon on June 19. The following individuals were present for all or part of the meeting.

Committee Members

W. Emmett Barkley, Howard Hughes Medical Institute
Martha C. Bohn, Northwestern University Medical School
Baruch A. Brody, Baylor College of Medicine
James F. Childress, University of Virginia
Neal A. DeLuca, University of Pittsburgh
David L. DeMets, University of Wisconsin Medical School
Theodore Friedmann, University of California, San Diego
Thomas D. Gelehrter, University of Michigan Medical School
Linda R. Gooding, Emory University
Larry G. Johnson, University of North Carolina, Chapel Hill
Philip R. Johnson, Jr., Columbus Children's Hospital
Terry Kwan, TK Associates
Maxine L. Linial, Fred Hutchinson Cancer Research Center
Bernard Lo, University of California, San Francisco
Madison Powers, Georgetown University
David Sidransky, Johns Hopkins University School of Medicine
Robert D. Simari, Mayo Clinic and Foundation
Diane W. Wara, University of California, San Francisco

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

RAC Executive Secretary
Stephen M. Rose, Office of the Director (OD/NIH)

***Ad Hoc* Reviewers/Speakers**
Jean Bennett, University of Pennsylvania
Mark B. Feinberg, Emory University
Gail E. Henderson, University of North Carolina, Chapel Hill
Nancy M.P. King, University of North Carolina, Chapel Hill
Bernard Moss, National Institute of Allergy and Infectious Diseases (NIAID)/NIH

NIH Staff Members
Elizabeth Adams, NIAID
Mary A. Allen, NIAID
Gwen Anderson, National Institute of Nursing Research

[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.

Lilia L. Bi, NIAID
Scott Cairns, NIAID
Fabio Candotti, National Human Genome Research Institute
Elaine Collier, National Center for Research Resources (NCRR)
Sussan Eftekhari, OD/NIH
Susan Emmett, OD/NIH
Suzanne Goodwin, OD/NIH
Laurie Harris, OD/NIH
Olivia Hess, OD/NIH
Robert Jambou, OD/NIH
Mary Joyce, National Heart, Lung, and Blood Institute (NHLBI)
Richard Knazek, NCRR
Cheryl McDonald, OD/NIH
Marina O'Reilly, OD/NIH
Alexander Rakowsky, OD/NIH
Gene Rosenthal, OD/NIH
Thomas Shih, OD/NIH
Allan Shipp, OD/NIH
Paul S. Sieving, National Eye Institute (NEI)
Sonia I. Skarlatos, NHLBI
Lana Skirboll, OD/NIH
Courtney Storm, OD/NIH
H. Eser Tolunay, NHLBI
Gisele White, OD/NIH

Others

There were 90 attendees at this 2-day RAC meeting. A full list of RAC members, *ad hoc* reviewers and speakers, and nonvoting/agency liaison representatives is included as Attachment I. A list of public attendees is included as Attachment II.

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

Dr. Friedmann, RAC Chair, called the meeting to order at 8:30 a.m. on June 18, 2003. Notice of this meeting as set fourth in the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on June 6, 2003 (68 FR 33960). The agenda for the meeting included in-depth review and discussion of a human gene transfer research protocol; an assessment of containment-level requirements for modified vaccinia Ankara pox viral vector; presentation of the quarterly data management report; a presentation of the findings of a study of the expectations of researchers and study participants involved in human gene transfer research; review of the current draft of the guidance on informed consent being developed by the RAC informed consent working group; discussion of the recommendations of the United Kingdom Gene Therapy Advisory Committee and the Working Party on Retroviruses; discussion of sessions on retroviral vectors held during the American Society of Gene Therapy annual meeting in June 2003; and identification of retroviral vector topics for presentations and discussions at future RAC meetings.

Dr. Rose reminded RAC members about the rules of conduct governing Special Government Employees, the screening process they undergo before each meeting, and the need to be attentive to conflicts of interest that could arise during the course of the meeting.

Dr. Rose explained that the Howard Hughes Medical Institute (HHMI) is producing an educational videotape on the ethical conduct of research. The HHMI requested and was granted permission by the Office of Biotechnology Activities (OBA) to videotape a portion of this RAC meeting to help explain the role of the RAC in enhancing the safe and ethical conduct of research involving recombinant DNA. The final videotape will be presented at a future RAC meeting.

II. Minutes of the February 10, 2003, Meeting/Drs. Friedmann and Powers

Drs. Friedmann and Powers noted that no substantive changes needed to be made to the February meeting minutes. Dr. Sidransky noted that there were a few minor edits that needed to be made and that he would convey them to staff by e-mail.

A. Committee Motion 1

The RAC approved the February 10, 2003, RAC meeting minutes, as amended, by a unanimous vote.

III. Minutes of the March 6-7, 2003, Meeting/Drs. Brody and Sidransky

No substantive changes were suggested to the March meeting minutes.

A. Committee Motion 2

The March 6-7, 2003, RAC meeting minutes were accepted unanimously.

IV. Presentation of NIH Award of Merit to Dr. Theodore Friedmann and Dr. Linda Gooding

Dr. Lana Skirboll, Associate Director for Science Policy, NIH, presented NIH Awards of Merit to Dr. Friedmann and Dr. Gooding, both of whom were completing their service on the RAC. Dr. Friedmann has served on the RAC since 1998 and assumed its chairmanship in August 2001. Dr. Gooding has served on the RAC since 2001. Dr. Skirboll, Dr. Patterson, and Dr. Friedmann all noted that the RAC represents the model of open public discussion of science.

Dr. Skirboll reported that staff in the NIH OBA and U.S. Food and Drug Administration (FDA) were awarded a Secretarial Distinguished Service Award in recognition of their role in the development of GeMCRIS, the gene transfer database which is regarded as a model approach to facilitate the reporting and analysis of adverse events in clinical research.

V. Discussion of Human Gene Transfer Protocol #0301-575: A Phase I Study of NT-501, An Implant of Encapsulated Human NTC-201 Cells Releasing Ciliary Neurotrophic Factor, in Patients With Retinitis Pigmentosa

Principal Investigator:	Paul A. Sieving, M.D., Ph.D., National Eye Institute, NIH
Additional Presenters:	Weng Tao, M.D., Ph.D., and William Tente, Neurotech USA, Inc.
Sponsor:	Neurotech USA, Inc.
RAC Reviewers:	Drs. DeLuca, L. Johnson, Linial, and Lo
Ad hoc Reviewer:	Jean Bennett, M.D., Ph.D., University of Pennsylvania

A. Protocol Summary

Retinitis pigmentosa (RP) is a group of incurable degenerative diseases of the retina. Approximately 100,000 Americans suffer from inherited degenerative RP. Although more than 100 RP-inducing mutations have been identified in several genes, there tends to be a common pattern of visual loss in patients with RP despite such genetic heterogeneity. To date, few available effective treatments exist for retinal degenerative disorders. One major difficulty in the development of treatments for this disorder has been the challenge of delivering agents to the back of the eye, in particular to the retina. To overcome this challenge, Neurotech USA, Inc., developed encapsulated cell technology called NT-501, that enables controlled, sustained delivery of therapeutic agents directly into the intraocular fluids, and thereby the retina. Because encapsulated cell technology devices can be retrieved, they provide an added level of

safety. The NT-501 encapsulated cell implant is engineered to deliver human ciliary neurotrophic growth factor (CNTF) to the eye. The goal is that the CNTF will arrest the progressive loss of photoreceptors that is characteristic of RP and related conditions.

The potential of growth factors as therapeutics for RP has been demonstrated in nonhuman animals. Among the growth factors studied, CNTF is reported to be the most effective in reducing retinal degeneration. An encapsulated device was developed to administer CNTF because systemic administration of the agents to treat RP was found to be impractical.

Each NT-501 unit consists of a sealed, semipermeable, hollow-fiber membrane capsule surrounding six strands of polyethylene terephthalate yarn that have been loaded with CNTF-secreting NTC-201 cells. The NTC-201 cells were derived from a human retinal pigment cell line. After the cells have been loaded, the ends of each capsule are sealed to secure the cells within the NT-501 unit. A titanium loop is attached to one end of the device and facilitates its placement and retrieval. The membrane allows CNTF to be diffused into the intraocular fluids. While the membrane does not block nutrients needed for the survival of the cells from entering, it does protect the cells from an immune response. The device is about 1.1 centimeters long, including the titanium loop, and will be placed well outside of the visual axis of the eye.

B. Written Comments From Preliminary Review

Twelve RAC members voted for in-depth review and public discussion of the protocol. RAC reviewers Drs. DeLuca, L. Johnson, Linial, and Lo and *ad hoc* reviewer Dr. Jean Bennett submitted written reviews, to which the investigators responded in writing and during this meeting.

While suggesting that the protocol appeared to pose no major risks to study participants, Dr. DeLuca requested more discussion by investigators of the following issues: the starting dose of CNTF; the stability and behavior of the cell line within the device; the nature and consequences of gene expression from the plasmid used to create the cells within the device; and the possibility and potential consequences of device failure following implantation. His major concern was about the presence of non-essential genes in the plasmid.

Dr. L. Johnson requested additional information about the following issues: use of prednisone prior to implant surgery; the mechanism by which CNTF prevents retinal degeneration and whether this information could predict possible toxicities; the significance of the mutant forms of CNTF described in the protocol; how safety of low doses will be assessed in order to proceed to higher doses; and the significance and long-term sequelae of the vitreous and lens changes. Dr. L. Johnson also suggested that post mortem studies include examination of the eye and that the protocol include a more thorough description of recruitment procedures. He also recommended that the informed consent document include information on the known toxicities of CNTF in the eye and other organ systems from prelinical and clinical studies and animal models and humans and a statement that the device contains genetically modified material.

Noting that no preclinical data on the consequences of device failure and cell leakage were included in the protocol, Dr. Linial asked whether such experiments have been conducted in nonhuman animals. Since the participants would require long-term administration, she also asked how long the cells in the NT-501 device would remain viable and producing CNTF and how the investigators would determine what effect replacement would have on the participant.

Dr. Lo expressed concern about the clinical significance of a decrease in amplitude of waves in the electroretinogram (ERG); the absence of preclinical data on gene expression in tissues other than the eye; and several aspects of the informed consent document including lack of clarity about the benefits and risks of the research, and the experimental nature of the study (through the use of such words as “treat” and “therapy”). He recommended that a description of the risks associated with the implant as distinct from the risks of surgery needed to be added as did a section on alternatives to the research.

Dr. Bennett expressed concerns regarding the safety of the NT-501 device and the effect of CNTF on the visual function of normal photoreceptors. She suggested further studies in large animal models. Regarding participant selection, she suggested that recruitment should focus on participants with similar disease and that genetic and clinical information about the participant's form of RP should be collected to enable correlation with any toxic or therapeutic effects of the intervention. Dr. Bennett asked whether it would be possible to obtain a small sample of vitreous or aqueous fluid at the time of implantation and explantation of the device to measure the amount of CNTF or antibodies. She suggested that the informed consent document state that development of a cataract after the NT-501 device is removed may require additional surgery. If the results of additional preclinical studies suggest that the function of some retinal cells could be impaired, such information would also need to be added to the consent.

C. RAC Discussion

The following additional questions and points were raised during discussion of the protocol:

- Dr. Friedmann asked whether toxicity studies have been conducted to determine the effect of a completely defective device, such as one that had been crushed or was otherwise without an intact semipermeable element.

- Dr. Bohn asked about the effect of CNTF on neuronal target cells such as the retinal ganglion cells, as well as other cell types in the retina.

- Dr. Bohn wondered how long the cells remain viable at room temperature and whether the amount of secreted CNTF is standardized.

- Dr. Simari asked about clinical experience with this device delivering other substances.

- Dr. Simari inquired whether the lack of immune response is related to the device or its intraocular location, and whether investigators are aware of or have experience with implantation of this device in nonocular sites.

- Dr. Sidransky was concerned about the risk of tumorigenicity in the eye. Although he agreed that the risk was small, he suggested that investigators might want to include reference to that risk in the informed consent document.

- Dr. Sidransky suggested that monitoring of vitreous fluid should be conducted before implant and at one point during implant at minimum, in addition to the planned monitoring at the point of implant and at explant.

- Dr. Brody asked for clarification about the role of Neurotech, USA Inc., in conducting the clinical trial and interpreting the resulting data.

- Dr. Borror suggested that a description of the dose-escalation study be included in the informed consent document, including the extent to which risks and potential benefit may vary by dose.

D. Investigator Response

Dr. Sieving brought a sample of the NT-501 device to the meeting so that RAC members could see it first-hand.

Dr. Tao explained that in previous studies, each of the hundreds of devices that have been implanted and removed over the years has been evaluated for integrity. In addition, worst-case scenarios have been simulated by direct injection of cells without the device, and tumorigenicity has been assessed through studies in immuno-compromised hosts. Results to date indicate that even a maximum number of

populating cells in the eye chamber caused only minimal cataract in the eye and that the cells are not tumorigenic.

Dr. Tao noted that investigators had monitored systemic immune responses against CNTF and the cells and found no response elicited against either. Investigators also have examined hundreds of explant devices for immunoglobulin, neutrophils, and macrophages and have found none within the devices.

Dr. Tao elaborated on the specifics of securing the device in the retina. Hundreds of devices have been anchored using a one-suture technique. After some long-term studies showed a small amount of fibrosis at the anchoring site, a change was made in the technique used to tie the knot in the loop that closes the sclera. No fibrosis has been associated with the modified anchoring technique.

Dr. Sieving explained that it would be difficult to capture changes in other cells in the retina, such as the retinal ganglion cells, because they are sparse in number and changes to those cells occur during the course of degeneration without intervention.

Dr. Tao explained that, although this device has never been used for ophthalmology diseases, the technology has been in development for more than 10 years and is currently in a Phase II clinical trial for treatment of chronic pain using bovine adrenal cells. Dr. Sieving noted that a device expressing CNTF has been implanted in the spinal columns of four human amyotrophic lateral sclerosis patients, and no systemic CNTF was detected in the participants.

Dr. Sieving explained that Neurotech USA, Inc., is only providing the experimental devices for the study. They will have no role in the conduct of the study or analysis of the resulting data.

E. Public Comments

Two representatives from The Foundation Fighting Blindness made comments about the protocol. Dr. Santa Tumminia, Director of Grants and Awards for the Foundation, explained RP and the importance of efforts to develop treatments and cures for blinding diseases. RP is considered a rare and orphan disease that strikes 100,000 to 200,000 Americans. She reported that the Foundation collaborated with Neurotech to test the NT-501 device in animal models of RP and that Neurotech's encapsulated cell device might offer ways to treat other diseases as well.

Ms. Lisa Mack, accompanied by her husband Steve Mack, described what it is like to live with RP. Two of their three young sons have been diagnosed with RP. She expressed the family's hope that this protocol would lead to the development of safe and effective treatments for RP and other retinal degenerative diseases.

F. RAC Recommendations

Dr. Friedmann summarized the RAC recommendations as follows and noted that they should be addressed prior to the initiation of phase II studies:

- Further research is needed to determine the effect of the CNTF-delivery device on the remaining functional photoreceptors. One possible approach to address this would be a large animal model with a recordable electroretinogram (ERG), i.e., the baseline ERG is not flatline.

- In order to fully appreciate potential adverse events associated with this product (the implantable device containing CNTF-secreting cells), it is important to analyze the effect of the product on other retinal cells such as Muller cells and retinal ganglion cells

- Non-essential sequences, such as the beta-lactamase gene, should be deleted from the plasmid in order to increase the safety of the gene transfer product.

- Since the device does not contain a clonal population of CNTF-secreting cells, the stability of the cells inside the device should be evaluated.

- Due to the wide variability seen in the clinical stages as well as the genetic cause of retinitis pigmentosa, safety and efficacy evaluations may be difficult to interpret from a non-homogeneous subject group. Considerations should be given to selecting a uniform population. The enrollment of a more homogeneous subject population in subsequent phases of this product's development may be important.

- A description of the recruitment plan and process should be added to the protocol.

- Inflammatory changes observed in the rodent studies are postulated as being due, in large part, to the surgical procedure and suturing technique. Thus, consideration should be given to involving a vitreo-retinal surgeon in the clinical studies in order to minimize potential inflammation from the implantation of the device. Such special expertise would also be useful for any additional animal studies.

- Samples of vitreal fluid should be obtained at the time of implant and explant, and consideration should be given to obtaining fluid at a midway point in the trial. This fluid should be analyzed for levels of CNTF, antibodies to CNTF, and for the presence of the other products expressed by the vector (e.g., beta-lactamase, VEGF).

- Since autopsies generally do not include examination of the eyes, the protocol should describe the specific eye studies that would be conducted as part of any autopsy performed in this protocol.

- It is not clear how predictive the changes in ERGs will be as a surrogate marker of CNTF effect. After completion of this phase of the trial, an update regarding the validity of this surrogate marker should be submitted to OBA.

- A written response to Dr. Bennett's review should be submitted to OBA.

- The investigator should confer with his IRB about the following recommended changes to the informed consent document and process:

    - The document should clarify that this is an experimental study and clearly distinguish the components of the study that are standard of care from those that are experimental in nature.
    - An explanation of the dose escalation should be provided.
    - The need for vitreous sampling and associated complications should be described.
    - In regard to potential adverse effects: (a.) tumor development should be listed as potential consequence of exposure to CNTF; (b.) potential for device breakage and associated complications should be described; (c.) animal studies have demonstrated that development of cataract is a possible adverse event. This finding, and potential need for cataract surgery, (and details about this procedure) should be detailed in the informed consent document.
    - Since it is the only other human trial evaluating CNTF use, consideration should be given to including information about the results of the Amyotrophic Lateral Sclerosis study that were described in the Investigator brochure and references cited therein.
    - The document should describe the role of the sponsor, Neurotech, in the study. If the investigator has any financial or other relationships to the sponsor that could pose a conflict of interest, they should be described as well.

G. Committee Motion 3

A motion by Dr. P. Johnson, which was seconded by Dr. Bohn, to approve these recommendations was approved 17 in favor, 0 opposed, and 0 abstentions.

VI. Data Management Report/Drs. Brody, Gooding, L. Johnson, Simari, and Wara

Dr. Simari noted that, since the previous RAC meeting, 12 protocols have been submitted to the OBA. The protocol just reviewed was the only one selected for in-depth review and discussion. A total of 569 trials are on file with the OBA; 41 are marking studies, 523 have therapeutic intent, and 5 are nontherapeutic trials. Of these 523, 367 target cancer, 57 target monogenic diseases, 39 target infectious diseases, 60 target other diseases and disorders. Four Appendix M-1-C-1 responses were submitted during this reporting period; these documents report on the investigator's response to the recommendations made by the RAC during its review. Dr. Simari noted that investigators took significant time and effort to respond to each of the RAC's individual recommendations and concerns.

A total of 111 adverse events (AEs) were reported to the OBA; 92 were initial reports, and 19 were followup reports. Of these, 12 were classified as "A1"—serious, unexpected, and possibly associated. Dr. Simari highlighted one of the followup reports from a Phase I safety study in patients with severe hemophilia B Factor IX (FIX) deficiency using adeno-associated viral vector to deliver the gene for human FIX into the liver. One participant received the adeno-associated virus vector expressing FIX via intrahepatic procedure and experienced transaminase levels that peaked at levels nine times normal between 4 and 5 weeks post-transfusion. After ruling out common causes of liver injury unrelated to the clinical study, the sponsor considered the possibility of immune-mediated response. Preclinical toxicology data from several species were reviewed, and at this and higher doses, no elevation of transaminases was identified that could be attributed to the vector or gene. Investigators will continue to monitor the subjects closely.

Dr. L. Johnson reported on an ongoing multicenter dose-response study to evaluate the efficacy and safety of Ad5.1FGF4 in patients with stable angina. Four months after entry into the trial, one participant developed an area of actinic keratosis with the focus of squamous cell carcinoma on the external right ear. Another participant developed an infiltrating lobular carcinoma of the right breast 6 months after study entry. Detailed information is not currently available regarding the relationships between the vector and these events, but the OBA continues to track them.

Dr. Wara presented a summary of protocol amendments and noting that 36 annual updates and 25 amendments were submitted to the OBA. Several amendments included changes to the informed consent document or reported the need to reconsent research participants as a result of the SAEs in the French X-linked severe combined immunodeficiency disease (X-SCID) study. Dr. Wara suggested that the attention investigators have given to modifying the informed consent process and to ensuring long-term followup of participants was a reflection of actions by the FDA and the NIH OBA, with advice from the RAC, about the two leukemia cases in the French X-SCID study.

She also reported on three amendments in a study of retinoblastoma using an adenoviral vector expressing thymidine kinase followed by ganciclovir administration. One amendment added dosing cohorts, the second modified the criteria regarding injections and inflammation, and the third was for a reentry study to allow participants to have a second round of injections. Information submitted in the admendments also noted that all participants had inflammation at the injection site in the vitreous but also some evidence of efficacy. She raised concerns that so many changes were made to a phase I study, especially since these changes were intended to maximize a perceived efficacy. Dr. Wara also highlighted a study of autologous human fibroblasts transfected with a vector expressing Factor VIII that reported that 7 of the 12 participants with hemophilia A showed decreased Factor VIII usage, reduced bleeding, and transient Factor VIII increase. Phase II studies are being planned for the trial.

Dr. Wara noted a significant increase in the number and complexity of the amendments that have been submitted and that many reflect substantive changes in the protocol and study design. She suggested several possible explanations for this increase: OBA staff are making significant efforts to obtain and analyze these amendments; changes reflect the fact that the field is maturing; and when new

observations are to be advanced, filing an amendment is easier than developing an entirely new protocol. It is important for the RAC to distinguish between amendments that reflect incremental changes in the study and those amendments that represent a significant difference from the original protocol.

A. Committee Motion 4

Dr. Brody requested a sense of the RAC in support of the development of a mechanism for requesting investigators, institutional review boards (IRBs), and institutional biosafety committees (IBCs) to respond to RAC comments regarding major amendments to protocols and that the RAC be informed about those responses in a manner similar to responses provided for review of initial proposals. In addition, Dr. Brody asked that the OBA report on the development of such a mechanism at a future RAC meeting.

In a motion put forward by Dr. Brody and seconded by Dr. Sidransky, the RAC concurred with Dr. Brody's request for the development of such mechanisms. The vote was 17 in favor, 0 opposed, and 0 abstentions.

B. Additional RAC Discussion

Dr. DeMets raised for discussion the question of how Phase I studies in human gene transfer are being defined with regard to safety, the number of research participants needed to achieve useful safety information, and the extent to which efficacy endpoints are also assessed.

Dr. Simek referenced FDA's description of a Phase I study. According to FDA, a phase I study is designed to assess the safety and determine the maximum tolerable dose of an agent.

Dr. Brody suggested that a mechanism is needed to help investigators determine the number of participants needed to answer the research question under study.

Dr. Simek suggested that statistically significant numbers are not likely to be reached in most phase I studies given recruitment challenges particularly for rare diseases.

Dr. Sidransky noted that very few toxicities were observed in preclinical gene transfer studies which contrasts with the preclinical experience in oncology drug development. The toxicities that have occurred in phase I studies, therefore, frequently were unexpected. He suggested that it may only be possible to consider the preclinical studies, the risk:benefit ratios and try to give the most useful advice.

Dr. Wara agreed that more stringency and precision are needed in defining the safety question to be analyzed in each protocol and the extent to which efficacy endpoints are to be assessed.

A member of the public, Dr. W. French Anderson, University of Southern California, commented that in the late 1980s, the RAC concluded after considerable discussion that phase I gene transfer studies were unethical if they were completely devoid of potential benefit. This is what led the RAC, he said, to assert that phase I studies should be termed PhaseI/II trials.

Dr. Brody noted that the RAC has been requesting removal of efficacy language or the suggestion of efficacy from informed consent documents on the assumption that Phase I GTR trials are only about safety. However, considering the discussion, efficacy language may have a place in some informed consent processes. Therefore, RAC discussion of the design and definition of Phase I GTR trials should also consider how such redefinition would impact the informed consent process.

Drs. DeMets and Rose suggested the formation of a working group on clinical trial design. The group could conduct some preliminary fact finding for a larger group on trial design that would include the FDA. The working group would be chaired by Dr. DeMets and staffed by Dr. Cheryl McDonald of OBA. Staff will prepare background materials for the working group, including its goals, questions to be addressed, and case studies illustrative of the issues. One outcome of the working group's efforts may be a proposal for the organization of a gene transfer safety symposium.

VII. Review of Selected American Society of Gene Therapy (ASGT) Annual Meeting Sessions Related to Retroviral Vectors/Dr. Friedmann

Dr. Friedmann reported on several sessions held at the June 2003 ASGT annual meeting that were related to retroviral vectors. The topics from those sessions included presentations on hematopoietic marking studies, ethical and policy dilemmas in clinical gene transfer studies, and the status of the French X-SCID clinical trial that reviewed the study, the lessons learned, and how the US and other countries responded to adverse events that occurred in the trial.

According to the presentation on the X-SCID study, the two participants who developed T-cell acute lymphoblastic leukemia (T-ALL) have successfully completed chemotherapy. One of the participants received an unrelated donor bone marrow transplantation (BMT), and the other participant is awaiting a BMT. To date no other participant has developed T-ALL including two who are more than 4 years postadministration. The French group is not planning to enroll new participants for approximately one year to allow time for further follow-up, to complete the integration site analysis, and to conduct animal studies of modified vectors.

In the United Kingdom, the Great Ormond Street Group has continued to enroll participants into their gene transfer clinical trial for X-SCID and to date no participants have experienced similar adverse events. In Germany, which had suspended all human gene transfer clinical trials involving retroviral vectors even before the adverse events in the French study, certain trials were allowed to resume enrollment (see Feb. 2003 RAC minutes for a presentation by Dr. Klaus Cichutek, Chair of the Commission for Somatic Gene Therapy, Paul-Erlich Institut, Germany). Italy has decided to determine whether to lift clinical holds on a case-by-case basis, and Japan has kept all SCID trials on clinical hold while allowing other gene transfer trials to proceed.

Also reported at the meeting was the outcome of an analysis conducted by an ASGT committee on Retroviral Mediated Gene Transfer to Hematopietic Stem Cells (HSC) of data from preclinical and clinical studies using retroviral vectors. No evidence of clonal expansion or integration near LMO-2 or other oncogenes was found. However, there were some limitations to the preclinical data analyzed. The animal models were usually not disease models, there was no selective advantage conferred by the transgenes (which appears to be the case in the French X-SCID study with gamma-chain transgene), and animals in most studies were not kept alive long enough to approximate the time of appearance of the T-ALL in the X-SCID clinical trial. The committee's full report is available on the ASGT Web site at www.asgt.org/reports/042003/.

A. RAC Discussion

Dr. Friedmann suggested that the RAC might want to revisit its recommendation that gene transfer should be attempted only in participants who are not eligible for or who have failed haploidentical BMT.

Dr. Wara proposed that the NIH organize a small symposium to allow the pooling of data on haploidentical BMTs in all forms of SCID and development of a consensus about it. She noted that guidelines in Europe, where there is more skepticism about the effectiveness of haploidentical BMT, are different from those in the United States. Dr. Friedmann agreed that the RAC should convene such a group. Dr. Rose stated that any such meeting would require collaboration with the appropriate NIH Institutes and Centers that support a large portion of the U.S. research portfolio in this area.

VIII. Recommendations of the United Kingdom Gene Therapy Advisory Committee (GTAC) and Committee on Safety of Medicines (CSM) Working Party on Retroviruses (April 2003)/Marina O'Reilly, Ph.D., NIH/OD

Dr. O'Reilly, OBA staff, reported on the conclusions reached by a joint working party of the GTAC and CSM which met in March 2003 to discuss the current knowledge regarding the risks of insertional

mutagenesis in retroviral vector-mediated gene transfer and to review the clinical trials in the United Kingdom (UK) using retroviral vectors. The meeting resulted in the issuance of 29 recommendations to the UK Department of Health. The first series of recommendations focused on areas for future research including retroviral integration preferences, effects of the gamma-c transgene expression, stem cell biology, the risks associated with endogenous retroviruses or elements in vector packaging cell lines derived from mouse cells, and modifications to vector design to increase safety.

Unlike the RAC, the working party did not suggest that haploidentical transplantation BMT should be preferred over gene transfer for X-SCID. A case-by-case assessment based on severity of disease, clinical condition, and availability and likely outcomes of conventional treatment was recommended instead. According to the working party report, a case-by-case analysis should also be used in determining the preferred approach in other studies of inherited diseases, but should not be extended to studies to cancer studies.

For future trials, the working group recommended that retroviral gene transfer into HSC should be limited to life threatening diseases for which there is no other acceptable treatment. For each study, preclinical studies should be performed to determine the expected number of integrations in the target cell and to determine the optimal number of integrations needed for efficacy. Monitoring of participants should include collecting as much molecular and cellular data as possible, particularly data about insertion sites of retroviral vectors. They did not recommend that currently healthy participants be subjected to more intensive monitoring or invasive procedures. However, all participants who received *ex vivo* retroviral vector gene transfer, not only those who have gone on to develop leukemia, should be monitored for the appearance of oligoclonal T cell populations and be followed long term. Samples should be collected, archived and stored in a standardized manner.

The working group recommended that consent be obtained for the retention, archiving and future use of samples from participants. For all retroviral vector gene transfer trials in the UK, the informed consent process should include information about the events in the French X-SCID trial. Lauding the French investigators for their openness in sharing information with the international community, the working party also recommended that the UK Department of Health establish mechanisms for data sharing of safety information across the international community.

IX. Retroviral Vectors: Topics for Future Presentations and Discussions at RAC Meetings/ Dr. Powers

In December 2002, the RAC discussed organizing a series of presentations at subsequent RAC meetings to explore topics regarding retroviral vector safety. Dr. Powers reviewed some of the topics proposed:

- State of the art of retroviral vectors and safety modifications that can be adopted in the clinic;
- Alternative integrating vectors;
- Issues in the development of new vector technology for clinical studies (e.g., animal models, FDA approval for human use);
- Retroviral vector integration: What knowledge is currently available? What technologies are available or could be developed rapidly to monitor integration events and sites of integration?
- Risk-benefit analysis: Is there a class of studies for which retroviruses should not be used or for which some exclusions should be in place?
- Modification to Appendix M: To ensure that all appropriate issues are considered, should a set of questions be added pertaining to the use of retroviral vectors?

- The need for an outcome assessment of the haploidentical BMT studies

- Development of appropriate large-animal models for certain kinds of diseases

Dr. Powers asked RAC members to convey to staff by e-mail which issues they believed should be taken up and in what priority order.

A. RAC Discussion

Dr. Rose suggested that the RAC invite Dr. Shawn Burgess, from the Genome Technology Branch at the National Human Genome Research Institute, to the September 2003 RAC meeting to discuss his study comparing integration of the murine leukemia virus (MLV) vector used in the French X-SCID study to human immunodeficiency virus-1. Apparently, a distinct difference was seen between the two viruses in integration pattern and frequency.

Noting that researchers are using the MLV retroviral vector because it has been studied extensively and approved, Dr. Linial said that she would be interested in learning more about how vectors are approved for clinical use.

Dr. Powers indicated that he would report back to the RAC at subsequent meetings on members' feedback about the list of proposed topics for further study.

X. Presentation of Indepth Assessment Regarding Containment-Level Requirements for Modified Vaccinia Ankara Pox Viral Vector/Dr. Barkley

Transgene, Inc. requested that the containment level for modified vaccinia Ankara (MVA) be changed from biosafety level (BL) 2 to BL1. Transgene is currently undertaking a clinical investigation using a vector derived from MVA that expresses the MUC-1 and IL-2 genes. The RAC team assembled to assess this request was chaired by Dr. Barkley and included three *ad hoc* consultants: Mark B. Feinberg, M.D., Ph.D., Emory University; Bernard Moss, M.D., Ph.D., NIAID, NIH; and Paul W. Spearman, M.D., Vanderbilt University [Dr. Feinberg, and Drs. Catherine Mathis and Patrick Squiban, Transgene Corporation, participated by teleconference. Drs. Moss and Spearman were not available.]

Dr. Barkley summarized his risk assessment and those of the *ad hoc* consultants, the differences between BL2 and BL1 containment, and RAC and CDC recommendations for containment of three other vectors derived from different attenuated pox viruses. Dr. Barkley concluded his presentation by noting that while there may be reasons to consider classifying the parental agent, MVA, as a Risk Group 1 agent, a comprehensive risk assessment should consider not only the parental agent but also how the agent is to be manipulated and any potential transgene product effects. For the MVA-MUC1-IL2 vector, a risk assessment should include consideration of the risks associated with large-scale vaccine production (e.g., quantity and concentration of the agent) and the potential for auto-immune responses to the MUC-1 transgene product.

A. RAC Discussion

Dr. Rose asked Drs. Catherine Mathis and Patrick Squiban of Transgene Corporation, Inc. to explain why adhering to BL2 containment was considered problematic. Their concern was with transferring the product from the vials to the syringe for injection into the participant in the clinical setting.

Dr. Barkley noted that it is often confusing to compare BL containment, which describes how materials are to be handled in the laboratory or in industrial settings, with how materials are handled by health care workers. The CDC has stated, in its vaccine recommendations, that the standard practices used in the health care field for administration of drugs and vaccines are appropriate and consistent with BL2 containment.

Ms. Kwan noted that IBCs should be able to advise site investigators about the appropriate method for handling these materials and asked whether the trial sites were receiving appropriate guidance from their IBCs and IRBs?

Dr. Squiban responded that the key unresolved question, at least in European trial sites, was whether BL2 required participants to be isolated. Dr. P. Johnson noted he was aware of that no data suggesting that a participant should be hospitalized or isolated.

Dr. Barkley suggested that the RAC consider forming a working group including clinicians and representatives of the CDC and the nursing community to provide guidance on the prevention goals at the BL2 level in the research setting and the application of BL2 practices to the health care setting. The product of such a subgroup would be an advisory note.

Dr. Lo noted that BL1 and BL2 designations were developed for the laboratory or production setting. In the clinical setting, a different set of guidelines and parameters is followed by doctors and nurses. The appropriate standards in the clinic should be applied relative to the perceived and actual levels of risk of the gene transfer research.

Dr. P. Johnson asked if the RAC considered the parental MVA virus to be appropriate for BL1 containment. Dr. Barkley responded that the parental virus, not having been derived by recombinant DNA techniques, does not fall clearly within the RAC's purview. The IBCs should conduct the risk assessments, review the requirements of the *NIH Guidelines*, and determine the appropriate containment level for individual sites. This process may result in a containment level for the recombinant vector that differs from the containment level associated with the risk group classification of the parental agent.

B. Public Comments

Ms. Gwen Anderson, a nurse currently on sabbatical at the National Institute of Nursing Research, NIH, stated that the predominant issue for nurses is the potential for infection. She noted that nurses, as frontline workers, trust the RAC to ensure the safety of everyone in gene transfer experiments and to make the best recommendations to local committees.

Ms. Mary Allen, NIAID, expressed concern that implementing BL2 precautions would require investigators to gown, glove, mask, and possibly administer the vector in a separate room. These types of required actions would reach far beyond universal precautions. Dr. Barkley responded that BL containment covers a range of practices to be implemented dependent on the risks associated with the agent and suggested that the RAC could work on providing some guidance to the clinical community on the application of the BL levels to clinical situations.

C. Committee Motion 5

Dr. L. Johnson made the following motion:
The RAC recommends that the *NIH Guidelines* regarding the administration and preparation of the MVA vector not be modified. The *NIH Guidelines* allow IBCs to raise or lower containment levels when they deem appropriate and IBCs should continue to be the source for addressing such questions. The motion was seconded by Dr. Powers and approved by the RAC in a vote of 17 in favor, 0 opposed, and 0 abstentions.

XI. Day One Adjournment/Dr. Friedmann

Dr. Friedmann adjourned the first day of the June 2003 RAC meeting at 5:15 p.m. on June 18, 2003.

XII. Day Two Opening Remarks/Dr. Friedmann

Dr. Friedmann opened the second day of the June 2003 RAC meeting at 8:30 a.m. on June 19, 2003.

XIII. Informed Consent: What Consent Forms Say and What Researchers and Study Participants Expect in Gene Transfer Research/Gail E. Henderson, Ph.D., and Nancy M.P. King, J.D., University of North Carolina, Chapel Hill

Dr. Gail E. Henderson and Professor Nancy King presented preliminary findings of a study of informed consent documents and research participant and investigator expectations regarding benefit in gene transfer research (GTR). Dr. Henderson explained the importance of studying benefit in GTR: Most studies are early-phase research (where informed consent challenges tend to be greatest), the oversight in the GTR field may have resulted in better consent forms and processes, and the unique social and scientific context of this area of research may affect expectations of benefit.

Telephone interviews were conducted between July 2000 and July 2002 with 39 investigators, 37 study coordinators, and 68 participants from 41 clinical gene transfer trials (of the 78 studies that were open for enrollment and eligible to participate in this research). The trials focused on different disease applications and most were early phase research. In the interviews with participants, the first question was "Why did you decide to join?" Only ten percent of participants responded that they joined to benefit others or society, 66% of participants indicated that they joined because they thought the study would be of benefit to them personally; the remainder of participants said they joined to help both themselves and others.

Of the GTR participants expecting direct benefit, half of these were tentative about the expectation. The type of response was related to many factors, including the participant's disorder, age, education, and prior research experience. In the principal investigator (PI) interviews, almost half of the PIs said they expected direct medical benefit for the participants. The responses did not correlate with disease indication or phase of research. PIs who expected direct benefit cited encouraging preclinical or clinical research as reasons for their expectations. PIs who did not expect direct benefit indicated that their studies were safety assessments and were not designed to detect efficacy.

Ms. King described the portion of the study related to consent forms and the consent process. From a sample of informed consent documents, the investigators analyzed the language used to describe potential for benefit. They examined how three different types of benefit – direct, ancillary and aspirational -- were described. Not only was there variation in the descriptions of benefit in different informed consent documents, there were variations within the same consent document in some cases. The variations occurred most often between the purpose and benefits sections. They also examined the terms used to describe the investigator and study personnel, the subjects, and experimental intervention. Some consent documents referred to the study investigator as the" investigator"; others used "physician." Subjects were called "subject", "participant", or "patient." References to the experimental intervention ranged from "intervention" to "therapy." Analysis of the results suggests that the consents can promote confusion about what to expect from the experimental intervention because important information is described vaguely, some terminology is inconsistent or contradictory, and different descriptions are used across sections of the documents. The study data led the investigators to make a number of recommendations to improve the informed consent process in GTR, including the following:

- Keep the informed consent document and process simple and clear.
- Describe direct benefit explicitly, including limits.
- Avoid vagueness and inconsistency of language; minimize "elegant variation."
- Describe the study design (especially dose escalation) to help participants recognize that they are not "patients."
- Use caution in offering study end points as potential direct benefits.

One of the most important outcomes of efforts to enhance the informed consent process would be to help participants distinguish hope from reasonable expectation. Greater clarity and understanding of expectations would help distinguish hopes from reasonable expectations about participation in GTR which would benefit everyone involved in this research.

A. RAC Discussion

Dr. Sidransky asked whether the research participants were queried about their satisfaction with the trials in which they participated. Dr. Henderson responded that although a specific question about satisfaction was not asked, overall satisfaction was usually described during the interviews. She also noted that the data showed that significant bonding occurs between the researchers and their participants.

Dr. Childress wondered what had been learned about the consent process as distinct from the informed consent document. Dr. Henderson explained that in response to a question about when participants decided to enter studies, 25 percent said they decided the same day they heard about the study. Some research participants indicated that their decisions were made even before the initial consent interview with the gene transfer researcher. In general, the data suggest that investigators recruit participants in very different ways.

Dr. Lo asked whether participants commented on the consent forms and whether best practices could be identified from this research that would help all gene transfer investigators in structuring their consent process. Dr. Henderson noted that determining best practices is an ultimate goal of this study, but the analysis was not complete yet. Preliminarily, it appeared that investigators who were very clear themselves about the goals of the study tended not to raise false expectations in study participants. Ms. King noted that they were planning to share any additional relevant information from the study with the RAC working group on informed consent in case it would be useful to the group in further developing the guidance on informed consent.

Dr. DeLuca asked whether there was a correlation between the subject's expectations and the benefit language used in the informed consent document. Ms. King responded that the consent forms and the interview results have not yet been correlated, but they would be soon.

Dr. Linial asked whether there was a correlation seen between expectation of benefit and the participant's clinical status. Ms. King explained that that analysis has not been done yet, in general that informed consent documents for cancer studies tended to include more treatment-related language than did the consents for other diseases. One possible explanation may be related to the fact that informed consent documents for cancer studies often attempt to adapt consents used in Phase III studies. Dr. Henderson also pointed out that because investigators and participants have different views of the concept of vulnerability, the extent to which clinical status is believed to affect expectations of benefit may need to be reconsidered. The impact of severity of illness on consent may be more complicated than is generally understood.

Dr. L. Johnson expressed concern that it would be difficult to develop a gold standard for consent language. For example, the French X-SCID trial was a Phase I trial in which there should have been no expectation of benefit but in which benefit did accrue to participants. Ms. King emphasized the importance of investigators, study coordinators, and IRBs and other oversight bodies being study-specific when improving informed consent documents and processes. Each trial will present its own set of criteria to determine the wording of informed consent, including phase, design, vector, route of administration, disease, and participants' severity of illness.

XIV. Informed Consent: NIH RAC Informed Consent Working Group (ICWG) Draft Guidance/Dr. Brody and Ms. King

Dr. Brody and Ms. King, co-chairs of the RAC informed consent working group, presented a progress report on the status of the development of guidance on informed consent for human gene transfer

research. The guidance is intended to be a web-based resource to supplement Appendix M-III and M-IV of the *NIH Guidelines*. The guidance will be available on the OBA web site. While PIs are intended to be the primary users, the guidance was written to be helpful also to IRB and IBC members, sponsors, potential research participants, and the public.

The guidance document is organized according to the sections of Appendix M-III and M-IV of the *NIH Guidelines*, and each section contains a box highlighting main points, samples of good consent language as well as problematic language, and links to relevant tools and background resources.

Comments on the draft guidance were obtained from PIs, sponsors, IRB and IBC members, consumers, and professional societies. The overall response was that the guidance was educational, easy to read, and well organized, but specific comments were also submitted. Some comments emphasized that the relationship between the guidance and other policy and regulation, particularly Appendix M, needs to be clarified to ensure its consistency with other Federal policies and regulations. Other comments suggested that the sample language may be misunderstood as required boilerplate rather than illustrative examples. Some comments recommended that the guidance concentrate on matters that are unique to gene transfer research. The co-chairs pointed out that Appendix M does not cover only issues unique to gene transfer and that the guidance should not either.

In addition to addressing these and other comments, the working group plans to continue improving the readability of the sample language. The working group will present the final web-based version to the full Committee, most likely in the fall.

Before beginning the discussion, Ms. King showed the Members what the guidance will look like when posted on the web and walked through its various sections and features.

A. RAC Comments and Discussion

Ms. Kwan suggested that the sample language be reviewed by a neutral party, possibly a middle school language arts instructor or a freelance editor of elementary and middle school textbooks. Such input would identify hard to understand words and concepts, as well as any instances in which the wording in the document is inconsistent. Ms. King agreed that this approach would be helpful.

Dr. Bohn was concerned about how to describe benefit in Phase I studies given that benefit of some kind, whether psychological, clinical, or societal, does accrue from participation in such studies. She requested additional discussion and consensus on this point. Ms. King acknowledged that, even if there is no direct benefit from the experimental intervention, one possible benefit to participants is closer monitoring of health. She also agreed that distinctions should be made between potential benefit to participants and benefit to society.

Discussion ensued about the appropriateness of the concept of Phase I/II trials. Dr. Brody noted that many investigators are pressing to be able to describe their trials as Phase I/II because they believe that therapeutic benefit is possible. Dr. DeLuca explained that even though extrapolation of positive results from animal studies as therapeutic benefit to humans is not always possible, investigators do decide to go forward and agencies decide to fund Phase I trials based on positive results in model systems that provide some degree of expectation of human benefit. Ms. King suggested that the differences between "benefit" and "efficacy" be clarified and included in the sample documents.

Dr. Gooding noted the need for language emphasizing that participants in studies will be treated differently from their previous treatment as patients. She offered an example of such language in the following: "Unlike the medical treatment you have received for your disease to date, the research intervention you will receive in this study will not be designed for your benefit. There will be no adjustments of dose to benefit you, but only to benefit the study."

Dr. Lo suggested that the RAC give further consideration to concepts such as benefit and assist the ICWG with drafting language. Relevant data from the King/Henderson study should also be incorporated

into the document. Dr. Brody agreed that the ICWG should work with the RAC members over the summer and present another draft at a subsequent RAC meeting. RAC members were also asked to use the draft guidance as they review protocols and consent documents over the next several months and to provide feedback to Dr. Brody or Ms. King about the completeness of the guidance in addressing issues in GTR.

Dr. Brody discussed the difficulties faced by participants who must read through long (30 pages or more) informed consent documents. He suggested that it might be preferable to include only the main points in the consent document and include the details as appendices.

Dr. Simari wondered about the legal and social implications of protocol changes after participants have signed an informed consent document. Determining when it is necessary to reconsent the participants would be specific to the study and situation. Ms. King noted that minors who are recruited through an assent process must go through an informed consent process when they reach age 18. Dr. Brody noted that the guidance document followed Appendix M, which does not contain a separate section on reconsenting. Ms. King suggested including more resources in the guidance document to provide information that would address other issues, such as reconsenting, which are not specifically covered in Appendix M.

Ms. King noted that the OBA is working on a brochure titled "Deciding Whether To Participate in Gene Transfer Research." This brochure will include a variety of background information on how gene transfer is performed. Among other uses, the brochure may be able to serve as a supplement to the informed consent document, thereby, allowing the consent to focus on the crucial aspects of the study itself.

B. Public Comments

Ms. Anderson, a nurse currently on sabbatical at the National Institute of Nursing Research, NIH, asked about the timing of the consent process. In some cases, participants may be consented several months before the study agent is administered, by which time their condition may have changed substantially. Dr. Brody agreed that the timing of consent was important and suggested that the draft guidance document be augmented to address this issue. Dr. Henderson responded that it is difficult to determine timing of consent.

C. Next Steps

Dr. Brody and Ms. King will continue refining the document, with substantial input from RAC members, for presentation at a future RAC meeting.

XV. Closing Remarks and Adjournment

Dr. Friedmann thanked the participants and adjourned the meeting at 12:00 noon on June 19, 2003.

[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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Stephen M. Rose, Ph.D.
Executive Secretary

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

Date:

_____

Theodore Friedmann, M.D.
Chair

Attachment I

RECOMBINANT DNA ADVISORY COMMITTEE

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Attachment II
Public Attendees

Julie Albertus, Genetics and Public Policy Center
W. French Anderson, University of Southern California
Nell Boyce, *U.S. News and World Report*
Tiffany Brown, FDA
Jan Chappell, AnGes, Inc.
Bernard Chauvin, Neurotech USA, Inc.
Bernard Davitian, Neurotech USA, Inc.
Jessica Friedman, American Association for the Advancement of Science
Joanne Hawana, *The Blue Sheet*
Giselle Hicks, FDA
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Attachment III
Abbreviations and Acronyms

ASGT	American Society of Gene Therapy
BMT	bone marrow transplant
BSL	biosafety level
CDC	Centers for Disease Control and Prevention
CNTF	ciliary neurotrophic growth factor
CSM	Committee on Safety of Medicines
ERG	electroretinogram
FDA	U.S. Food and Drug Administration
FIX	Factor IX
GTAC	Gene Therapy Advisory Committee
GTR	gene transfer research
HFM	hollow-fiber membrane
HHMI	Howard Hughes Medical Institute
IBC	institutional biosafety committee
ICWG	Informed Consent Working Group
IRB	institutional review board
MLV	murine leukemia virus
MVA	modified vaccinia Ankara
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	Office of Biotechnology Activities, NIH
OD/NIH	Office of the Director, National Institutes of Health
PI	principal investigator
RAC	Recombinant DNA Advisory Committee
RP	retinitis pigmentosa
SAE	serious adverse event
T-ALL	T-cell acute lymphoblastic leukemia
X-SCID	X-linked severe combined immunodeficiency disease