RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 4, 5, and 6, 2002

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]

December 4-6, 2002

The Recombinant DNA Advisory Committee (RAC) was convened for its 88th meeting at 1:00 p.m. on December 4, 2002, 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 1:00 p.m. until 4:45 p.m. on December 4, from 8:30 a.m. until 6:00 p.m. on December 5, and from 8:30 a.m. until 10:45 a.m. on December 6. 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
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, National Institutes of Health (NIH)

Executive Secretary
Stephen M. Rose, NIH

***Ad Hoc* Reviewer**
John Iacomini, Ph.D., Massachusetts General Hospital (via teleconference)

Speakers
Fabio Candotti, National Human Genome Research Institute (NHGRI), NIH
Dale E. Hammerschmidt, University of Minnesota
Sue L. Levi-Pearl, Tourette's Syndrome Association, Inc.
Harry Malech, National Institute of Allergy and Infectious Diseases (NIAID), NIH
Jennifer Puck, NHGRI, NIH
Christof von Kalle, Cincinnati Children's Hospital Research Foundation
Kenneth Weinberg, Children's Hospital of Los Angeles

[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.

Nonvoting/Agency Liaison Representatives
Kristina C. Borror, U.S. Department of Health and Human Services
Stephanie L. Simek, U.S. Food and Drug Administration (FDA)

NIH Staff Members
Thomas Bauer, Jr., National Cancer Institute (NCI), NIH
J. Scott Cairns, NIAID
Sarah Carr, Office of the Director (OD), NIH
Javier Chinen, NHGRI
Cindy Dunbar, National Heart, Lung, and Blood Institute (NHLBI), NIH
Kelly T. Fennington, OD
Suzanne Goodwin, OD
Kailash Gupta, NIAID
Laurie Harris, OD
Beverly Hay, NHGRI
Dennis Hickstein, NCI
Valerie Hurt, Office of the General Counsel, OD
Robert Jambou, OD
Ken Kuramoto, NHLBI
Robert Lanman, OD
Cheryl McDonald, OD
James McNamara, NIAID
Rita Misra, NCI
John C. Morris, NCI
Marina O'Reilly, OD
Alexander Rakowsky, OD
Gene Rosenthal, OD
Alan Schechter, National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK, NIH
Shepherd Schurman, NHGRI
Thomas Shih, OD
Allan Shipp, OD
H. Eser Tolunay, NHLBI
Gisele White, OD

Others

Approximately 60 others attended this 3-day RAC meeting. A list of the attendees appears in Attachment II.

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

Dr. Friedmann, RAC Chair, called the meeting to order at 1:00 p.m. on December 4, 2002. Notice of this meeting as set forth in the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on November 21, 2002 (67 FR 70234). This meeting involved a presentation and discussion of informed consent and monitoring issues concerning an adverse event (AE) in a gene transfer clinical trial, review of four protocols, an update from the NIH RAC working group on informed consent in human gene transfer research, data management safety information and clinical reports.

Dr. Rose referred the RAC members to the NIH Rules of Conduct and Conflict of Interest notice provided in their briefing materials.

II. Minutes of the September 19-20, 2002, Meeting/Dr. Barkley and Ms. Kwan

Dr. Barkley and Ms. Kwan reviewed the draft September 2002 RAC meeting minutes. Two minor wording changes were suggested, but otherwise the draft minutes were an accurate representation of the meeting. Dr. Barkley recommended that the draft minutes be accepted.

A. Committee Motion 1

It was moved and seconded that the RAC approve with two suggested revisions the September 2002 RAC meeting minutes. The vote was unanimous in favor.

III. Data Management Report/Drs. Simari and Wara

In the reporting period of August 1 through October 31, 2002, 31 serious adverse events (SAEs) were reported to the OBA, 24 of which were classified as serious and possibly associated with the gene transfer.

In the reporting period of August 1 through October 31, 2002, 80 annual reports or amendments were provided to the OBA, the majority of which added or deleted sites or investigators. Three amendments set forth plans for long-term followup, ranging up to 15 years. Dr. Wara discussed an amendment that was instituted following an SAE in the trial involving a Phase I trial of nerve growth factor for Alzheimer's disease. One participant developed intracranial bleeding and died. The PI placed the study on hold and undertook an extensive evaluation of the protocol, including obtaining formal external reviews. Seven fairly substantial changes have been made to this protocol, including changes in the stereotactic needle, a modified approach in advancing the needle, and maintaining all subjects under deep anesthesia to minimize movement during surgery.

IV. An Adverse Event in a Gene Transfer Clinical Trial for X-Linked Severe Combined Immunodeficiency Disease

In a trial at the Necker Hospital for Sick Children in Paris, France led by Dr. Alain Fischer, eleven children with X-linked severe combined immunodeficiency disease (X-SCID) received gene transfer involving *ex vivo* transduction of CD34+ cells with a retroviral vector expressing the gene for the common gamma chain of the IL-1 family of receptors. Nine participants experienced significant restoration of their immune systems. In August 2002, one research participant developed a leukemia-like illness approximately three years after gene transfer. In the expanded T cell clone, the retroviral vector had integrated into and activated *LMO-2*, a proto-oncogene. While the development of cancer due to insertional mutagenesis was known as a theoretical risk of retroviral vector usage, this was the first report of such an event.

To prepare for the RAC meeting, a planning session was held on October 29, 2002, in which several RAC members and experts in the field reviewed the SAE and identified salient issues for RAC discussion including the following:

- What further analyses should be done on the specimens from the affected subjects, as well as from the other subjects in this study? What results are still pending and how will these affect the ultimate analysis of this adverse event?
- Choice of integrating vs. non-integrating vectors, safety modifications to retroviral vectors such as use of self-inactivating (SIN) vectors, tissue specific promoters, insulators, or suicide mechanisms, mechanisms for site-specific integration.
- What type of monitoring is necessary, how frequently, and for how long? Should tissues be archived to enable future monitoring?
- What information should be provided about this SAE during the consent process? In which protocols should the consent be modified? How can this information be disseminated to participants enrolled in current studies and those who have already participated?

A. Case Presentation and Followup/Christof von Kalle, M.D., Cincinnati Children's Hospital Research Foundation

[In addition to presenting the molecular analysis of the SAE, Dr. von Kalle also presented the clinical case on behalf of Dr. Alain Fischer, who was unable to attend the meeting.]

X-SCID results from the deficiency of the common gamma chain (gamma-c) of the interleukin-2, -4, -7, -9, -15, and -21 family of receptors. T cell differentiation is blocked along with the development of functional B cells. To date, the treatment of choice is stem cell transplantation, with high rates of survival (80-90%) in HLA-identical transplants but only approximately 60 percent survival when haplo-identical transplants are done. However, poor T-cell function results in some cases and many patients continue to need immunoglobulin augmentation due to incomplete B-cell differentiation.

The gene transfer clinical trial has to date enrolled and treated 11 research participants. Nine of the 11 participants showed rapid normalization of the CD3 T-cell numbers with functional T cell immunity and improved B cell immunity. The fourth participant was the youngest to receive gene transfer and developed T and B cell immune responses. A varicella zoster virus (VZV) infection was cleared at 30 months. The participant's gamma-delta-T cells increased from 7,000 per microliter to 80,000 per microliter, progressing to a leukemic state with more than 300,000 cells per microliter in the peripheral blood, anemia and splenomegaly at month 34. The gamma-delta T cell clone contained a single integrated retroviral vector and a 6:13 chromosomal translocation. When the cells reached 300,000 cells per microliter, chemotherapy for childhood leukemia was begun.

Retroviral vector integration was analyzed by the LAM-PCR method. In the gamma-delta T cell clone, a single proviral insertion occurred within the first intron of the *LMO-2* oncogene. Interpretations of the data include the following: (1) Insertional mutagenesis led to aberrant expression of the LMO-2 RNA, (2) aberrant gamma-c signaling may be involved, (3) the VZV infection may have played a role, and (4) a genetic susceptibility to cancer existed in the family (two childhood medulloblastomas, one in a sibling and one in another relative.) Ongoing investigations include the mechanism of *LMO-2* deregulation, retrospective clone tracing, an overall profile of the gene expression, and examination of VZV replication and transcription. All participants in this trial are now being screened for clonal dysregulation by various immunological and molecular assays, and a comprehensive analysis of the integration sites will be coupled with an investigation of the frequency of at-risk integration sites in each participant.

1. RAC Discussion

Dr. L. Johnson asked about the importance of the propensity for childhood malignancies in the family. Dr. von Kalle responded that the familial cancer history does not bear any direct relation to leukemia, but the family history does play an important role because the *LMO-2* expression only produces a premalignant phenotype, to which other events must be added to produce cancer.

Dr. von Kalle explained that there is no evidence to date for VZV gene expression in the gamma-delta T cells, but the episomal status of the VZV genome is still being studied.

B. Review of the BRMAC Meeting/Stephanie L. Simek, Ph.D., FDA

Dr. Simek reviewed the FDA's considerations regarding the SAE and summarized the October 10, 2002, Biological Response Modifiers Advisory Committee (BRMAC) meeting on this topic. At the meeting, Drs. von Kalle and Fischer presented, as did experts in the fields of SCID treatment, retroviral insertional mutagenesis, *LMO-2*, and investigators involved in related clinical trials.

The discussion at the BRMAC meeting centered on whether there are additional data or measures that clinical investigators need to provide before current and future SCID gene transfer clinical trials proceed in the United States. Committee members considered each of the following as they pertain to X-SCID and other forms of SCID:

- The risk-benefit of gene transfer vs. alternative therapies: During the discussion, it was noted that many cancer treatments carry a risk of secondary cancer. The BRMAC suggested that a family pedigree may need to be conducted to characterize all subject populations, which could suggest a predisposition to cancer such as defect in a tumor-suppressor gene. The consensus of the BRMAC was that this type of trial should be allowed to proceed especially in light of the successful results seen to date with this study compared to the poor results seen in cases where haplo-identical BMT is attempted.
- Revisions to informed consent documents to inform current and potential participants about the possible risks associated with retroviral gene transfer: The BRMAC agreed that all consent forms in retroviral vector trials should include information about this SAE with an explicit statement that the gene transfer caused the leukemia.
- Alterations to the cell dose: Rather than studies of cell dose, the BRMAC suggested that further research should be done on targeting human stem cells since CD34 cells might not be the appropriate hematopoietic target.
- Alterations to the vector dose: Vector dose is more likely to become a significant issue with novel vectors such as lentiviral vectors, that have integrated with higher copy numbers in cells.
- Mapping of vector insertion sites on all clinical lots of cells prior to release for clinical use: Although the BRMAC agreed that insertion-site mapping prior to lot release was not currently technically feasible, it was strongly recommended that followup analysis of participant samples be conducted. Close monitoring for outgrowth of a single clone is needed; such monitoring would allow investigators to determine the frequency of monoclonal outgrowth in relation to the development of cancer. Once a monoclonal integrant is observed, it should be sequenced, and additional phenotypic analysis should be performed. Knowledge of the integration site may inform clinicians about the appropriate treatment and may allow for earlier treatment. The BRMAC recommended 3 to 6 months as the time interval for mapping and rejected archiving samples in lieu of real time testing. If integration is not observed, further testing would not be necessary. For each protocol, investigators should develop a monitoring plan that includes a trigger point for additional analysis. However, some flexibility should be allowed in developing monitoring plans, and under some circumstance, it should be possible to justify not implementing extensive plans.
- Alterations in vector design: The BRMAC concluded that development of preclinical models is needed to assess the risk of vector insertion for new vector designs such as SIN vectors. Although SIN vectors are safer in some aspects, they still have the potential to integrate into a suppressor gene, thus interrupting the function of that gene.

After considering the BRMAC recommendations, the FDA took the following actions: (1) requested revisions, along the line suggested by the BRMAC, to the informed consent documents in all clinical trials using retroviral vectors, and (2) requested that sponsors using retroviral vectors designed to target stem cells develop monitoring plans to analyze participant samples for vector integration clonality.

1. RAC Discussion

Dr. Linial asked whether the BRMAC or the FDA made any recommendations about exclusion from trials based on family pedigree. Dr. Simek stated that a complete family pedigree is usually not available and cannot be required. Although the BRMAC did discuss excluding participants with a family history of cancer, it was merely suggested that family pedigree information might be helpful in preventing an oncogenic event. Dr. Gelehrter noted that the research participant's unusual family history of two cases of medulloblastoma would raise concerns of familial predisposition to cancer. He expressed hope that participants will be forthcoming with pertinent family history information. He did not suggest that family history of cancer should be an exclusion criterion, particularly in gene transfer for lethal diseases without therapeutic options.

Dr. DeMets expressed, however, concern about altering the informed consent documents to state that this gene transfer caused leukemia. Adding such strong language to a consent form would go beyond the current knowledge about the causation of the SAE. Dr. Simek replied that the BRMAC's consensus was that it had heard no evidence that the leukemia was not caused by the retrovirus.

Dr. Weinberg explained that, epidemiologically, medulloblastoma and childhood leukemia are linked in two ways: They co-occur in family histories, and they occur as second malignancies for each other in children who have been treated for one. He pointed out how difficult it would be to deny therapy to a child with leukemia because it increases the risk of medulloblastoma.

Dr. Sidransky noted that only a few hundred families in the world exist in which two first-degree relatives have medulloblastoma, and only one or two families in the world exist in which X-SCID and medulloblastoma have co-occurred. This suggests that there may be a predisposing factor involving a tumor suppressor gene in the family. While the *LMO-2* insertion contributed to the development of the clone, to say it caused the disease is not supported by the molecular biology.

C. Background Information on Adverse Events in Retroviral Vector Studies/Dr. Rose

Dr. Rose presented background material from the OBA's protocol database on retroviral vectors used in gene transfer clinical trials and specifically in the SCID trials. Within the total of 558 protocols registered with OBA, 181 used retroviral vectors. Retroviral vectors were the only systems used for the first 3 years of gene transfer trials, and were used in the first protocols for marking, cancer, and infectious disease. Retroviral vector usage has decreased in recent years; in 2002 only 11 percent of protocols employed retroviral vectors and these were primarily in cancer and infectious disease indications. Historically, retroviral vectors have been used for a wide range of clinical indications. In the majority of protocols *ex vivo* administration was used and targeted hematopoietic cells. In the 181 total protocols, none of the SAEs that have been reported have been considered by the investigator to be associated with the gene product.

Dr. Rose provided data on the SCID protocols (both, those registered with OBA and those done in Europe and Japan). These are X-SCID (5 protocols/15 research participants), ADA-SCID (5 protocols/26 research participants),and *Jak3*-deficient SCID (1 protocol/1 research participant). A total of 42 research participants have been treated. All are Phase I studies, and all have used retroviral vectors. The protocols vary in terms of age range of participants, transduced cells, use of bone marrow conditioning, and in the ADA-SCID trials, use of polyethylene glycol-modified bovine ADA (PEG-ADA).

D. Adverse Events in Clinical Trials Using Retroviral Vectors/Alexander Rakowsky, M.D., OBA, NIH

Dr. Rakowsky reviewed an analysis of data from OBA's database on relevant SAEs in other retroviral vector studies. Dr. Rakowsky described the scope of the data in the OBA database. The OBA database consists of data from studies that are subject to the *NIH Guidelines* as well as studies that have been submitted voluntarily. It does not capture data from international studies or studies that are not subject to NIH oversight. In addition, annual reports have not been submitted for all studies.

Of the 181 studies employing retroviral vectors, eight relevant SAEs were found. Relevant SAEs for this purpose were defined as malignancies, myelodysplastic syndromes, and monoclonal or any other type of proliferation. Four lymphomas were found in studies targeting human immunodeficiency virus [HIV]). Two cases of myelodysplastic syndrome occurred in a breast cancer study and a neuroblastoma study. One monoclonal lymphoproliferation occurred in an HIV study. One malignant glioma occurred in a brain tumor study.

E. Monitoring Research Participants in Clinical Trials Using Retroviral Vectors/Drs. Friedmann and Wara, Moderators

1. Presentation by Dr. Rose

The monitoring studies performed in the X-SCID gene transfer clinical trials can inform proposed monitoring plans for other gene transfer trials. It may not be possible to obtain useful information regarding the integration sites prior to infusing *ex vivo* gene-modified cells, because too much product

sample would be used up in conducting such analysis. Instead, archiving cells for future analysis may provide more useful information.

The participants at the Oct. 29 planning session suggested the following questions could assist in the formulation of monitoring plans for other clinical trials:

- What other types of trials use retroviral or integrating vectors?
- What roles do the phase and type of gene transfer clinical trial have in the frequency and duration of monitoring (e.g., potentially therapeutic trials vs. marking studies)?
- What role does the age of the research participant have in the monitoring plan (i.e., children vs. adults)?
- What role does the gene transfer procedure itself have in the monitoring plan (e.g., hematopoietic stem cells vs. nonhematopoietic stem cells)?
- What role do these factors have in collecting, analyzing, or archiving samples such as peripheral blood, bone marrow, stem, and skin cells?

2. Presentation by Kenneth Weinberg, M.D., Children's Hospital of Los Angeles

Dr. Weinberg discussed proposed changes to the monitoring process developed by the group of investigators at CHLA conducting an ADA-SCID study and an X-SCID study. The plan was developed following consultation with the FDA and several local review boards. He noted potential insertional oncogenesis was considered in previous monitoring plans, but those plans had focused on assaying for replication competent retrovirus (RCR).

The monitoring protocol described by Dr. Weinberg represents a prospective plan to accomplish what was done following the SAE in Dr. Fischer's study. The goals of a monitoring plan for gene transfer research protocols are to:

- Provide adequate monitoring so that determination of the need for therapeutic intervention is made as expeditiously as possible
- Ensure that research participants are not exposed to either physical or psychological harm from unnecessary interventions
- Characterize any leukemias occurring in gene transfer trials
- Determine whether any observed leukemias resulted from insertional mutagenesis
- Characterize the clonality of hematopoiesis after retroviral gene transfer of hematopoietic stem cells, a research goal that is not necessarily related to participant safety

The major features of the monitoring protocol proposed by Dr. Weinberg and his colleagues include:

- Routine prospective monitoring of the clonality of the integrants in lymphohematopoietic cells by linear amplification-mediated (LAM) PCR, to be conducted in collaboration with Dr. von Kalle
- Routine monitoring for clinical signs of abnormally growing populations of cells
- Detailed characterization of peripheral or marrow populations if indicated by increasing predominance of a retroviral integrant clone or evidence of abnormal hematopoiesis
- Criteria for intervention based on clinical and laboratory evidence of leukemia
- Lifetime monitoring

To monitor clonality, the protocols call for using LAM-PCR every 6 months to assay vector integrants, starting 3 months after transduction. Increasing oligoclonality or monoclonality would trigger an earlier clinical evaluation, including blood counts, chemistries, and evaluation for lymphoproliferation. If no evidence of leukemia was uncovered, the LAM-PCR would be repeated every 3 months for 2 years until there is either evidence of stabilization of the integrant's representation within the population of transduced cells or the individual develops a defined leukemia. Routine monitoring would continue throughout the individual's life.

Regarding techniques for characterizing increasingly prevalent or abnormal clones, Dr. Weinberg discussed two methods: (1) sequencing of the LAM-PCR product to determine the site of integration and (2) analysis of the immunophenotype to assign a lineage to the cell population present. If the cells were found to be lymphoid, molecular and immunologic methods would be used to determine immunoreceptor gene expression or usage, which could then be used to characterize clonality.

Diagnostic questions related to analyzing increasingly prevalent or abnormal clones would include:

- How is leukemia defined?
- Is there a cytogenetic abnormality present in the cells?
- Is the integrant near a proto-oncogene or any other gene that might cause dysregulation of a cell?
- Is there abnormal differentiation of the cells?
- Does the population growth of the clone stabilize?
- Is there evidence of abnormal hematopoiesis or cells arrested at a particular stage of differentiation?
- Is the integrant present in cells of multiple hematopoetic lineages, as evidenced by molecular analysis?

Dr. Weinberg cautioned that, even though the malignancy in this case developed in a lymphoid population, it should not be assumed that malignancies triggered by insertional oncogenesis could not occur in nonlymphoid populations.

3. RAC Discussion

Dr. Friedmann focused the discussion on whether changes or additions regarding monitoring need to be made to Appendix M in the *NIH Guidelines*.

Dr. Sidransky stated that, although LAM-PCR is currently the best approach to measuring the clones, it is important to allow other methods to be used. LAM-PCR is promising, but it needs to be better defined for clinical use.

Dr. Candotti pointed out that lifetime monitoring is not a new concept. Dr. Simek explained that the FDA had required lifetime follow-up for retroviral vector trials with archiving after the first year if samples are RCR negative. Recently the BRMAC has recommended 15 year follow-up for all gene transfer studies.

Dr. Dunbar noted that most trials have an official end date, and it is unclear who would pay for the equipment and staff time needed to follow research participants for the remainder of their lives.

Dr. Hammerschmidt stated that long-term monitoring must include contingency plans since investigators may retire or die during the course of the trial.

Dr. DeMets suggested that a structured, systematic method of collecting data must be put in place to prevent loss of data when the investigator retires or moves.

Dr. von Kalle envisioned a broad database to ascertain the frequency of insertion into the regions of proto-oncogenes and clonal dysregulations, but he wondered how many patient followup years and how many clones would be needed to ascertain SAE frequency.

Dr. Wara suggested that the RAC consider recommending to the NIH that a gene transfer centralized databank and a centralized sample archive system be developed. Without these resources, specific recommendations are not likely to be useful. She also suggested that a statement should be added to Appendix M requesting investigators to propose a long-term monitoring program for their studies.

Dr. Sidransky agreed that archiving samples would be critical because prospective monitoring is currently complicated and expensive. When rare events occur, investigators can do lookback studies only if

samples have been archived. Dr. Simek explained that the BRMAC did not oppose archiving, but it did not think archiving should take the place of testing.

Dr. Lo suggested that the following questions be added to Appendix M: What clinical follow-up will be done? Are there plans for archiving specimens? Are certain AEs expected in your study given such factors as underlying disease or mechanism of the gene transfer, and therefore, will prospective monitoring be needed?

V. Day One Adjournment/Dr. Friedmann

Dr. Friedmann noted that this afternoon's discussion would be continued during the morning of Day 2 of this RAC meeting. He thanked the participants and adjourned the first day of the December 2002 RAC meeting at 4:45 p.m. on December 4, 2002.

VI. Day Two Opening Remarks/Dr. Friedmann

Dr. Friedmann opened the second day of the December 2002 RAC meeting at 8:30 a.m. on December 5, 2002.

VII. Continuation of Discussion: An Adverse Event in a Gene Transfer Clinical Trial for X-Linked SCID

A. Informed Consents for Clinical Trials Using Retroviral Vectors/Drs. Childress and Powers, Moderators

1. Presentation by Dr. Weinberg

Dr. Weinberg presented the efforts of a consortium of investigators to modify the informed consent documents of two SCID protocols (ADA and X-SCID). The risk of leukemia from gene transfer should be discussed in context with the other potentially severe complications that are already included in the informed consent process. Providing an estimate of the risk of leukemia is difficult. It is not obvious whether the relevant denominator is the number of participants in the X-SCID trials, all types of SCID trials, or all trials using retroviral vectors in hematopoietic stem cells. Because of this problem, the investigators chose not to provide a quantitative indicator of risk.

Regarding causality, the investigators decided to state that leukemia could occur as a result of the gene transfer. The discussion of the mechanism of leukemia induction by vector insertional oncogenesis would be incorporated into the existing discussion of the potential for leukemia development due to RCR. An important distinction would be made given that the risk of RCR induced leukemia can be reduced by screening gene transfer preparations and using only preparations not contaminated with detectable RCR, whereas reducing vector-associated risks such as insertional mutagenesis is not currently possible.

2. Presentation by Dr. Dale E. Hammerschmidt, M.D., FACP, University of Minnesota

Dr. Hammerschmidt explained the danger in conflating (1) the information that is reasonable to present to research participants with the information that should be in the informed consent document, (2) the informed consent process with the informed consent document, and (3) the risks and benefits of participating in a clinical trial with the risks and benefits of receiving treatment. He then discussed the basics of the informed consent process in ethical human subject research. Requirements for ethical human research include a valid and important scientific question, valid methodology, balance between risks and benefits to the participant or society, independent ethical review (i.e., an institutional review board [IRB]), and an informed consent by the person bearing the risk. Fully informed consent may not be obtainable, but it is a goal—for sociological, ethical, and legal reasons.

In order to determine whether the risk-benefit balance is acceptable, the research participant must understand what is going to happen, how what is going to happen is different from what would happen while being treated outside of the study, the inherent risks of the study, possible benefits, and the voluntary nature of participation. Possible obstacles in accessibility of this process are the complexity of information; complex and confusing presentation of the information; dilution of important concepts in a sea of detail (e.g., a long informed consent document that can obscure the risk information); conflation of therapy and research; therapeutic misconception; unregulated, misleading information (e.g., Web sites, news stories, and advocacy groups); and confusing the informed consent document with the informed consent process. The large universe of information that should be available to research participants is different from information that should be presented to them; an even smaller universe comprises information that should be included in the informed consent document. The universe of information that the research participant actually understands and retains is smaller yet and is a moving target.

Risk is an actuarial construct with several major components, including severity, likelihood, duration, and latency of the possible harms and "proportional causality" i.e., how likely the harm is to be caused by the procedure or by the substance to which the person is being exposed. In the case of the SAE experienced by the subject in the X-SCID study, the leukemia seems to be severe and causally related. However, latency, frequency and duration can only be extrapolated from this one case.

Dr. Hammerschmidt reported that he asked two members of his staff who have master's degrees and are medically sophisticated to review the proposed strawman language. Both individuals found the language difficult to understand. He suggested giving research participants or their surrogates as much detail as they want and can understand, providing all participants with complete background information as part of the consent process, while keeping the required language in the informed consent document short and to the point. He suggested that rather than providing specific wording for IRBs, appropriate minimum language should be provided. He suggested language along the following lines:
A research participant in this study has developed leukemia and has required treatment.

- The investigators think the gene transfer made the leukemia more likely to happen.
- It is too early in the study to know whether this is a rare or common event.
- It is too early to know the severity of the leukemia or the medical outcome for the child who developed leukemia.
- Enough information indicates that others in the trial are doing well, so the risk of participating in this trial is deemed reasonable at the present time.

Regarding how this information should be disseminated, Dr. Hammerschmidt suggested that it should be included in (1) the informed consent document and informed consent process for new enrollees, (2) a verified informational update for current enrollees in gene transfer trials for X-SCID, and (3) forms and informational updates for new and current enrollees in other trials of retroviral gene transfer (with appropriate modifications). For some studies and diseases, it may not be as clear as in this X-SCID trial that the risk-benefit balance remains favorable.

Ethical informed consent will be achieved if information is presented in the informed consent document in simple terms, if fuller background information is made available to anyone who wants it, and if researchers admit that they are trying to do their best in the face of a great deal of uncertainty and ambiguity.

3. RAC Discussion

In response to Dr. Friedmann's query about how much information provided during the consent process is retained by research participants, Dr. Hammerschmidt provided anecdotal statistics from his personal experience: In the renal transplant clinic at his institution, he interviewed 10 individuals before finding 1 who had read the informed consent documents before signing. Other studies have followed individuals at 48 hours, 2 weeks, and 1 year after receiving informed consent and have found that, at the 1-year interval, 15 percent of individuals no longer even remembered that they had participated in a research study. In response to a follow-up question, Dr. Hammerschmidt indicated that focus groups of patients have been used in some studies to develop the informed consent documents. Dr. Hammerschmidt

routinely solicits feedback from research participants after they have undergone a procedure, and his institution has asked groups of patients to read prepared documents for their accessibility.

Dr. Lo pointed out how important it is to convey uncertainty and admit that some causalities and outcomes are not known or understood, but that further research will reduce the uncertainty. He discussed the importance of helping research participants and their families understand the big picture of issues while providing access to detailed information if desired. Dr. Lo also wondered whether a test of assessment of basic understanding should become part of the informed consent process. For example, research participants are sometimes asked to rephrase the main features of the study to ensure understanding.

B. RAC Discussion: Monitoring and Informed Consent

In lieu of further review of the strawman language, Dr. Friedmann suggested that the basis for this discussion be the points suggested by Dr. Hammerschmidt's five points be used as a starting point for the development of RAC recommendations about what additional information should be included in the informed consent process.

1. RAC Discussion on Point 1: "A research participant in this study has developed leukemia and has required treatment."

RAC members agreed that "leukemia" is what the SAE should be called. Less definitive descriptions such as "leukemia-like" were rejected.

Drs. Lo and Sidransky suggested adding language about the participant's family history of childhood cancer. Dr. Simari agreed but suggested that it be added to one of the other five points.

2. RAC Discussion on Point 2: "We think that the gene transfer made the leukemia more likely to happen."

Dr. Puck suggested deleting "more likely," since it was the BRMAC concluded that the gene transfer caused the leukemia to happen.

Ms. Kwan discussed the popular understanding of the word "cause," which is a direct, single-line relationship between two events. This does not fit in this case. Dr. Sidransky agreed, noting that the gene transfer was necessary but not sufficient to cause the leukemia in this case. Dr. Weinberg noted that the preponderant evidence is that gene transfer caused the leukemia. On this point, Dr. Lo suggested that the statement focus on explaining that gene transfer was "a cause" rather than "the cause" of the leukemia. Dr. Friedmann suggested saying "The introduction of this vector and this gene worked together with the predisposing factors to cause the leukemia," thus recognizing the multiple factors at work as well as the crucial role of the gene transfer product.

3. RAC Discussion on Point 3: "It is too early in the study to know whether this will be a rare event or a common one."

Dr. Gelehrter suggested adding wording to indicate that "other predisposing factors may alter this risk" and that, in this case, there was varicella infection and a family history of childhood cancer.

4. RAC Discussion on Point 4: "It is too early to know how well the child with leukemia will do."

There was no disagreement with this statement.

5. RAC Discussion on Point 5: "Enough children in the study have had improved immune function that we think it is still appropriate to continue the study."

Dr. Weinberg pointed out that his IRB would view this language as coercive because it is difficult for research participants (or, in this case, their parents) to make a distinction between "the study should go on" and "you should enroll your child in the study." Investigators at UCLA have been forbidden to use of this type of language.

Ms. Kwan suggested that the aim of the discussion should be to determine the RAC's conclusions about the event, not to develop language for a document. However, Dr. Lo noted that RAC reasoning and deliberations could also be used as a guide to help other people think through the issues.

Dr. L. Johnson suggested stating that most of the children in this study have shown significant reconstitution or improvement of immune function, rather than stating that participants should continue in the study. Dr. Barkley proposed adding "without evidence of leukemia".

Dr. Sidransky suggested splitting Point 5 into two points, one of which would acknowledge that the RAC believes these studies should continue.

Dr. Lo expressed concern about the "improvement of immune function" wording because some of the transplant data show that immune function declines in the long term and that intravenous therapy is still needed to keep immunity at a minimal level. Dr. Puck suggested adding the caveat that these are preliminary results. Dr. L. Johnson noted that immune function was significantly improved even if there is a reduction in transgene expression several years in the future.

Discussion ensued regarding whether this statement referred to only the X-SCID studies or the other SCID studies as well. The initial general agreement was that Point 5 would relate to all X-SCID gene transfer studies. Dr. Weinberg pointed out that the FDA put a clinical hold on all SCID studies in the United States, and trials for other forms of SCID and even other diseases have been put on hold in other countries. He asked whether the RAC wanted to make a broader recommendation.

Dr. Linial pointed out the need to differentiate between the Paris X-SCID study and other planned studies, which perhaps should go forward but not on the basis of the improved immune function observed in the Paris study, because the outcome in other studies may not be similarly positive. In this regard, Dr. Puck suggested wording as follows: "In view of this single adverse event, the RAC does not believe that stopping all retroviral gene transfer trials is warranted."

Dr. Simari and Dr. Powers recommended adding another bullet point that would say that, in light of this AE, some modification of informed consent documents in current and future trials is appropriate. He also suggested adding wording about monitoring and long-term followup for ongoing trials.

6. RAC Discussion Regarding Other SCID (Non-X-SCID) Trials

Regarding the ADA-SCID trial in Italy, Dr. Candotti reported that four research participants were enrolled and treated. Of the first two participants, one has experienced complete immune reconstitution; results on the first two participants were published in *Science* in September 2002

Dr. Linial noted that the risk analysis for ADA SCID gene transfer would differ from X-SCID because there is an alternative form of treatment. Because of this, she felt that only X-SCID trials should be addressed by the RAC at this time.

Dr. Friedmann reminded RAC members that the public and the gene transfer field are looking to the RAC for guidance not only on X-SCID studies but also on similar disorders; silence on non-X-SCID trials would not be helpful.

Dr. Linial suggested changing the wording from "retroviral vectors" to "obligate integrating vectors" to ensure that all integrating vectors that might be used in the future would be covered by the RAC's recommendations.

Dr. P. Johnson suggested that there appears to be no reason not to address the other SCID studies with regard to whether they should proceed. Dr. Simari suggested considering the non-X-SCID trials with all the other retrovirus studies that use hematopoietic stem cells rather than considering all the SCID trials together. Dr. Friedmann disagreed, suggesting that it is reasonable to presume that all the SCIDs will behave similarly under similar conditions. Dr. Weinberg noted that the one biological feature that has made all the SCIDs so attractive for initial trials is the selective advantage of transduced cells.

Dr. Powers expressed the need to be cautious about stating clinical improvements in non-X-SCID trials and in recommending their resumption, because the RAC does not have enough information about the benefit in these studies.

C. Summary of RAC Recommendations and Next Steps Regarding X-SCID Studies

The following language regarding the SAE in this X-SCID gene transfer trial was crafted with general agreement among RAC members:

- A research participant in this experimental study developed leukemia and has required treatment
- It is the NIH RAC's considered conclusion that the gene transfer was a cause of the leukemia;
- It is too early in the study to know whether this will be a rare event or a common one; predisposing factors may have contributed to this result;
- It is too early to know how the child with leukemia will do in the future.
- The majority of children in this X-SCID gene transfer study have had major clinical improvement to date;
- The NIH RAC finds that resumption of X-SCID gene transfer studies is justified, contingent upon appropriate informed consent process and monitoring plan modifications.

D. Summary of RAC Recommendations and Next Steps Regarding Non-X-SCID Studies

The following language was crafted relative to the RAC's position regarding non-X-SCID gene transfer trials:

- With regard to other SCID gene transfer studies, some participants experienced mild to moderate clinical improvement.
- The NIH RAC finds that resumption of other SCID gene transfer studies is justified, contingent on appropriate informed consent and monitoring.

1. Sense of the RAC 1

It was moved and seconded that the two bullet points listed above represent conclusions of the RAC regarding non-X-SCID clinical trials. The vote was tied: 8 in favor, 8 opposed, and 1 abstention.

E. Additional Discussion at the March 2003 RAC Meeting

Dr. Rose indicated that further discussion and review of additional data would occur at the next meeting of the RAC in March 2003.

VIII. Discussion of Human Gene Transfer Protocol #0210-556: A Phase I, Open-Label, Dose-Escalation Trial Evaluating the Safety and Immunogenicity of Sequential Administration of Recombinant Deoxyribonucleic Acid (DNA) and Adenovirus Expressing L523S Protein in Patients With Early-Stage Non-Small Cell Lung Cancer (NSCLC)

Principal Investigator:	John J. Nemunaitis, M.D., US Oncology
Presenter:	Martin A. Cheever, M.D., Corixa Corporation
Sponsor:	Corixa Corporation
RAC Reviewers:	Drs. Childress, DeLuca, DeMets, and L. Johnson

Ad hoc Reviewer: None

A. Protocol Summary

The proposed study is a phase I trial to evaluate recombinant DNA and adenovirus expressing the L523S protein (pVAX/L523S and Ad/L523S, respectively) as a prime-boost vaccine strategy in patients with early NSCLC. The primary objective of the trial is to determine the safety of a vaccine regimen consisting of a fixed dose of pVAX/L523S followed by Ad/L523S with dose-escalation through three cohorts in patients with early NSCLC who have undergone primary resection of the lung tumor within the previous 12 months. Additionally, this trial will assess the extent to which antibody and/or cell-mediated immunity (CD4+ and/or CD8+) specific for the L523S protein will be elicited by the vaccine regimen.

The L523S DNA-adenovirus immunotherapeutic vaccine targets a lung-cancer associated protein in order to prevent recurrence. The immunogenic protein is L523S. The vaccine product contains two components, plasmid DNA containing the L523S gene (pVAX/L523S) and a recombinant adenovirus-5 containing the L523S gene (Ad/L523S). pVAX/L523S is designed to initiate and stimulate (prime) an immune response to the L523S protein, which is found to be highly expressed in lung carcinomas. Ad/L523S will be used to expand and enhance (boost) the effectiveness of the response to pVAX/L523S.

The rationale for the use of both DNA and adenovirus as immunizing agents is based on their proven ability to elicit strong cell-mediated responses, particularly cytotoxic T lymphocytes (CTL) to recombinant antigens. Administering DNA first is expected to generate a weak initial response sufficient to prime CD4+ and CD8+ lymphocyte populations recognizing L523S epitopes. The subsequent administration of an adenovirus construct containing the L523S gene is expected to boost the initial immune response by favoring the expansion of primed CD4+ and CD8+ T cells. Priming with DNA and subsequent boosting with recombinant adenovirus, or other recombinant viruses, has been found to be an effective method to generate a powerful humoral and cellular immune response.

The proposed clinical protocol is a phase I, open-label, safety and immunogenicity study of a fixed dose of pVAX/L523S followed by ascending doses of Ad/L523S, in three cohorts of patients with stage IB or II NSCLC who have undergone primary surgical resection of the lung tumor within the previous 12 months. The pVAX/L523S and Ad/L523S will be administered separately by intramuscular injection at separate time points.

B. Reviews by RAC Members

Drs. Childress, DeLuca, DeMets, and L. Johnson submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Childress concentrated on the informed consent document. He suggested some sentence restructuring to make the document simpler to read, and changes to some language to minimize the risk of the “therapeutic misconception”. Several of the less novel procedures pose some risk to participants (e.g., blood draws), and this information should be included in the informed consent document. Request for consent to autopsy was not mentioned in the original form but has been added. Some inconsistent wording in the original version of the protocol regarding lactation and the number of participants has been addressed.

Dr. DeLuca asked whether there are additional safety concerns to be considered for participants with prior immunity to the L523S protein and would prior immunity affect analysis of the immune response following vaccination. Because so little is known about the function of L523S, except that it is an mRNA binding protein possibly involved in embryonic development, he asked whether studies had been performed to determine the possible effects of overexpression of the L523S protein from the Ad and plasmid. He asked about the possibility of vaccinating with a version of the protein lacking the RNA binding domain. Regarding the preclinical experiments, Dr. DeLuca expressed concern about the appropriateness of the experiments relative to the proposed clinical application. Mice were vaccinated with L523S plasmid, adenovirus, both or none, and challenged with L523S transduced tumor cells.

Smaller tumors were observed in the vaccinated mice. In order to more closely approximate the situation in participants, he asked whether it would be possible to perform experiments in which tumors were established prior to vaccination. Because similar tumor reduction occurred with vaccination of plasmid alone, compared to combination with adenovirus, he asked why the protocol did not use only plasmid vaccination since there are additional safety concerns with adenoviral vectors.

Dr. DeMets asked what would happen if the maximum tolerated dose (MTD) was not reached in the third cohort. Would a phase II trial proceed at the highest dose even though it may not be the MTD? He noted that many analyses are intended for data collected from relatively few participants, so the results should be interpreted carefully for both false-positive and false-negative results.

Dr. L. Johnson noted several areas of concern in his review: (1) the use of the L523S antigen in research participants with existing immunity; (2) the rationale for the inclusion criterion requiring that female participants not bear children in the future; (3) since endogenous expression of the L523S protein has been detected in ovary, fallopian tube, colon, bronchus, tonsil, gallbladder, and pituitary gland, these organs may be predisposed to immune-mediated destruction if induction of an immune response is successfully induced; (4) the survival benefit detected in the mice in the tumor challenge experiment; (5) the amount of blood proposed to be collected from participants; and (6) the pending multiple-dose toxicology data in cotton rats and nonhuman primates and the biodistribution data in cotton rats.

C. RAC Discussion

Several concerns were raised by RAC members in addition to those expressed by the primary reviewers:

- Dr. L. Johnson suggested that female participants be required to use contraception during the trial, and be monitored for long-term immune response. If none is detected, then precautions about conceiving should be lifted. Dr. Sidransky suggested that women participants in this clinical trial not get pregnant for up to 2 or 3 years after participation.
- Several RAC members asked whether additional animal models would provide useful information regarding the proposed human trial. Dr. Gooding noted that the design of using DNA followed by a viral vector expressing the same protein is being used in many other vaccine trials currently under way. Therefore, the paucity of preclinical data may be less concerning because of the currently available human data from these other trials.
- Dr. P. Johnson asked the investigators to characterize the preexisting immune response.
- Dr. P. Johnson suggested that investigators limit enrollment to people who are either Ad seronegative or have neutralizing antibody titers of less than or equal to 1:200 against adenovirus type 5.
- Dr. Sidransky asked the investigators why they were not considering adding participants with advanced cancer.

D. Investigator Response

Dr. Cheever acknowledged the importance of Dr. DeLuca's concern about the lack of preclinical data regarding antitumor efficacy. He stated that the animal models establish clearly that the proposed regimen is immunogenic, that the immune response is specific, and that cytotoxic T cells can kill the tumor. Investigators could not analyze survival benefit because the mice are required to be sacrificed when tumors reach a predetermined size. Dr. Cheever noted that animal models are important for delineating parameters of immune response, but they are not helpful for examining antitumor responses that could be extrapolated to human experience. Comparing the vaccine regimens in mice was not informative because, while DNA elicits an effective immune response in mice, it is much less effective in humans. In response to Dr. Friedmann's suggestion about doing a human xenograft study, Dr. Cheever noted that human xenografts cannot be used because they only grow in immune-incompetent mice, which cannot be vaccinated due to their lack of immunity.

Regarding Dr. DeMets' question about what would happen if the dose-escalation design did not identify a maximum tolerable dose (MTD), Dr. Cheever explained that for conventional cancer chemotherapy, Phase I drug studies continue until a toxicity level is reached, and then efficacy studies are based on a

lower dose than that. Vaccine studies, such as the one proposed, attempt to elicit an effective immune response with the expectation that the level necessary to produce that response will not be toxic.

In response to concerns raised about research participants who have preexisting immunity, Dr. Cheever noted that in general, cancer patients with a tumor immune response tend to do better than those who do not have that immunity. Preexisting immunity to L523S has been characterized to the extent that investigators know that an antibody response and a T-cell response exist; the number of cytotoxic T cells has not been quantified.

Regarding the prohibition of child bearing for female participants, Dr. Cheever explained that the concern was fetal wastage. If antibodies to L523, which may be involved in fetal development, are able to cross the placental barrier, they could have an unknown effect on the fetus. While the investigators expect that the antibody response will attenuate over time, it is not known whether the antibody levels would increase during pregnancy. Dr. Cheever also explained that the majority of research participants will be past their childbearing years, so conception is not likely to be a frequent issue.

In response to Dr. Sidransky's question about including individuals with more advanced disease, Dr. Cheever explained that giving the vaccine to individuals with advanced disease, in whom there is no expectation of an adequate immune response (because of the disease stage), may not be informative regarding safety issues.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations:

- Since pre-existing immunity to adenoviruses may interfere with the development of an immune response to the transgene, thereby confounding interpretation of this trial endpoint, the trial design should be modified to limit participation to research participants who have neutralizing antibody titers of less than or equal to 1:200 against adenovirus type 5.
- The informed consent document should clearly explain the reason for the inclusion criterion requiring that female participants "agree to use adequate contraception (barrier methods, oral contraceptives) throughout the study and must plan not to bear children in the future." Alternatively, the inclusion criterion could be modified to exclude women capable of bearing children from the trial or to allow the possibility of child bearing following contraception use for 2 or 3 years post-trial participation if monitoring detects loss of the immune response to L523S.

G. Committee Motion 2

It was moved by Dr. L. Johnson and seconded by Dr. Bohn that the above two recommendations expressed the recommendations of the RAC. The vote was 15 in favor, 1 opposed, and 0 abstentions.

IX. Discussion of Human Gene Transfer Protocol #0210-557: A Double-Blind, Placebo-Controlled, Dose-Escalation Pilot Study To Assess the Safety and Effects of AMG0001 in Patients With Ischemic Heart Disease Not Amenable to Coronary Artery Bypass Graft or Percutaneous Coronary Intervention

Principal Investigators:	Michael Simons, M.D., Dartmouth-Hitchcock Medical Center, and Brian H. Annex, M.D., Duke University School of Medicine
Sponsor:	AnGes, Inc.
RAC Reviewers:	Drs. Lo, Sidransky, and Simari
Ad hoc Reviewers:	None

Dr. Simari disclosed that he is a PI on two collaborative research grants funded by Boston Scientific, which is providing the delivery catheter for this protocol; however, neither of his grants involves the use of the experimental catheter used in this proposal.

A. Protocol Summary

Ischemic heart disease (IHD) due to atherosclerosis is the most common underlying cause of cardiovascular disability and death in the United States. The American Heart Association estimates that 12.6 million Americans have IHD, and more than 500,000 die from the disease every year. The lifetime risk of developing IHD after age 40 is 49 percent for men and 32 percent for women. The primary symptom of IHD is angina pectoris (pains in the heart). A number of approved medications (including nitroglycerin, beta-adrenergic blocking agents, and calcium-channel blocking agents) can improve symptoms by reducing myocardial oxygen demand, but no currently available medication can restore the compromised arterial blood supply. Invasive therapies and surgical procedures are reserved for high-risk patients and patients who are unresponsive to standard medical therapies. Medical therapies for IHD are generally successful in controlling the symptoms of the disease, but even optimal therapeutic regimens do not prevent the eventual worsening of IHD.

Therapeutic angiogenesis is a method under investigation for inducing the growth of new blood vessels in order to improve blood flow to ischemic areas of the heart or other areas of compromised vascular flow such as in peripheral artery disease (PAD). Hepatocyte growth factor (HGF) is similar to vascular endothelial growth factor (VEGF) in that it stimulates the growth of blood vessel cells, but it differs from fibroblast growth factor (FGF) in that it doesn't stimulate the growth of smooth muscle cells or fibroblasts. Because HGF has many biochemical and physiological activities that are believed to influence angiogenesis, AnGes, Inc. is currently evaluating HGF in patients with severe PAD in a Phase I/II study in Japan and has proposed this study to evaluate HGF in patients with coronary artery disease (CAD).

The proposed study has two stages. The Phase I study will be a dose-escalation safety study that sequentially evaluates four doses of HGF DNA plasmid administered via intramyocardial injection. The intramyocardial injection is to be performed with an experimental transendocardial catheter under development by Boston Scientific. In stage I of this trial, 8 participants will be evaluated at each of the four dosage levels: 6 will receive plasmid HGF and 2 will receive a placebo. Escalation of dose will depend upon the occurrence of defined dose-limiting toxicities. Three doses with acceptable safety will be compared to placebo in the Phase II portion of this study. Up to 60 participants will be randomized to either placebo or one of the three doses of plasmid HGF. The sponsor anticipates that the Phase II portion of the study will assess the safety of the three doses and provide some initial data regarding the effect of plasmid HGF on the perfusion of ischemic areas of the heart.

B. Reviews by RAC Members

Drs. Lo, Sidransky, and Simari submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Lo raised concerns about the safety of subjects randomized to placebo in the Phase I portion of the study. He suggested it would be preferable to separate the Phase I and Phase II components of the study, using a randomized design in Phase II after dosage and toxicity have been studied. He noted that the inclusion criteria need to be more specific, especially with regard to the issue of a participant's suitability for revascularization procedures. He also questioned whether patients with chronic viral hepatitis should be excluded from the Phase I study given their increased risk for hepatocellular carcinoma. He also noted that the efficacy endpoints need to be more clearly defined. Dr. Lo observed that the consent process should make it clear that the injections will be done with a new catheter and that though all participants will undergo a cardiac catheterization and intramyocardial injection, some will receive a placebo injection. Also, he noted that the consent document should not characterize the transfer of DNA to the heart muscle as "harmless," when the risk is actually unknown.

Dr. Sidransky questioned the use of the ameroid constriction model in the preclinical studies because this produces a large single lesion while the clinical entity to be studied is more likely to be diffuse disease. He noted that no pathological data on the two animals that died, after having received plasmid, were submitted for review and that more preclinical data would have been helpful. He raised questions about dosage and randomization selection and some of the inclusion and exclusion criteria. Dr. Sidransky also questioned the justification for the administration of saline given the invasive nature of the injection.

In his written review, Dr. Simari noted that the preclinical data was submitted as a work in progress without final results and that complete results would have been more helpful. He pointed out that no data were provided about the investigational catheter or its compatibility with the gene transfer product. He also raised concerns about the use of a placebo in the Phase I portion of this protocol and noted that the consent form should clearly represent the human experience with the delivery system, including its risks. He noted that the qualifications and relationships of the independent reviewers to the investigators should be clearly delineated, and the investigators' relationships to the sponsor should be disclosed as well.

C. RAC Discussion

The following questions and concerns were raised during the RAC discussion of the protocol:

- Dr. Lo questioned whether a nuclear medicine imaging test might be warranted as opposed to or in addition to an exercise treadmill test given that baseline EKG abnormalities may make the results of treadmill testing difficult to interpret. He also questioned whether there should be continuous cardiac monitoring for 24 hours to detect any possible arrhythmias after injection rather than just a 12-lead EKG.
- Dr. Sidransky urged the investigators to reconsider the design of the study. The use of a placebo group, particularly in the Phase I arm, is essentially testing only the safety of the catheter. To assess the safety of the catheter plus the gene transfer product versus the safety of the catheter alone would require a different study design.
- Dr. Gelehrter also questioned the use of a placebo in this trial.
- Dr. Simari asked the investigators to submit safety data on the catheter from trials conducted in Europe.
- Dr. Simari asked about the background incidence of melanoma in the Sinclair pigs and its relevance to the use of HGF and subsequent development of melanoma in two of the animals in the preclinical studies.
- Drs. DeMets and Lo expressed concern about the statistical power of the study design given with the small numbers of participants and the three to one ratio of study agent to placebo.

D. Investigator Response

In reply to the questions about treadmill testing and cardiac monitoring, Dr. Simons stated that the exercise stress test is a standard test and is low risk to the patients. In this context, the exercise time is the primary evaluation point, and the ability to read the EKG for changes would be a secondary endpoint. The cardiology community no longer considers thallium stress testing useful in this patient population. The participants will be in the hospital and will be on full cardiac monitoring for 24 hours post-injection.

Regarding the use of a placebo control in this study, Dr. Simons gave a brief historical perspective of previous therapeutic angiogenesis trials, and indicated that the investigators in this field believe that open label studies are worthless due to bias among both the investigators and the participants. The sponsor and investigators believe that the use of a placebo arm and blinding will help to provide better assessment of the safety parameters.

With respect to concerns regarding the safety of intramyocardial injections, Dr. Simons explained that scar formation from the needle injection could be expected, but that it would be minor compared to the amount of scar tissue already present due to disease. The risk that additional scarring could bring about an arrhythmia is not significant but will nonetheless be monitored.

Regarding the issue of the melanomas in the Sinclair pigs, Dr. Simons reported that although the lab that conducted the safety study was aware that the Sinclair pig has a 30 percent incidence of melanoma, the investigators were not aware of this. The investigators did not think the melanomas were related to HGF because HGF was not detected in serum and plasmid was not detected in any organs other than the heart. In addition, one animal was later found to have a melanoma before the HGF was administered. The next safety study will be conducted in Yorkshire pigs, which do not have a high rate of melanomas.

In response to Dr. Simari's questions about the catheter, Dr. Simons explained that the device is under an IND for use in the United States and has been used in a number of clinical studies mostly in Europe and Canada. He agreed to provide the results from these studies.

E. Public Comment

Dr. Zhi Feng Long from Anges, Inc. noted that the Sinclair pig was a well-characterized animal model of human melanoma and had been used for that purpose in the late 1970s and early 1980s.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations:

- The use of a placebo group in the Phase I study poses an unjustifiable risk to the research participants who would be randomized into that study arm. The RAC strongly recommends this study be redesigned without the use of a placebo arm.
- The investigators should confer with their Institutional Review Board (IRB) and, if applicable, the institutional conflict of interest committee about any recommended changes to the informed consent documents and process.
- The qualifications and role of the independent reviewer in determining who is referred for the study versus who receives standard clinical care should be clarified in the protocol. This is particularly important with respect to the determination of patient eligibility criteria of "not well suited for revascularization by CABG or PCI." The protocol should clearly delineate that the principal investigator will not make this determination, present the study or the standard treatment options to the patient, or carry out the consent and enrollment processes.

G. Committee Motion 3 and Request for Followup

It was moved by Dr. Sidranksy and seconded by Dr. Gelehrter that these recommendations expressed the comments and concerns of the RAC. The vote was 15 in favor, 0 against, and 0 abstentions.

Dr. P. Johnson requested that the RAC receive a report of the final action of the local IRBs involved in this protocol.

X. Continuation of Discussion: An Adverse Event in a Gene Transfer Clinical Trial for X-Linked SCID: Informed Consent Issues

A. Results of ADA-SCID Trials/Dr. Candotti

Dr. Candotti provided additional information the ADA SCID trials. In the ADA form of SCID, patients do not have B or T-cell functions. Similar to patients with X-SCID, they die early in life unless their immune system is reconstituted by bone marrow transplantation. Data reported at a recent meeting indicates that a total of 2,045 ADA-SCID patients have been treated with bone marrow transplantation in Europe since 1990. A minority of those patients had a human leukocyte antigen (HLA) identical sibling donor, and in all cases in which there is an HLA identical donor match, bone marrow transplantation is the therapy of choice. However, when an identical HLA donor is not available and a partially HLA matched transplant is performed, the survival rate is only approximately 24 percent. The transplantation using partial HLA

matched donors is even less successful with ADA-SCID than with X-SCID. The United States experience is similar to the experience in Europe.

For patients who do not have a matched related donor, enzyme replacement therapy (PEG-ADA) is available. PEG-ADA is slow-released in the serum and detoxifies the deoxyadenosine metabolites by passive transfer. This therapy works in four out of five cases by providing protective but not normal T-cell function. Approximately 50 percent of patients on PEG-ADA recover B-cell function. The protein in the injected PEG-ADA is bovine, so all patients develop antibodies against that protein as soon as the immune system is restored. In 10 percent of patients, these antibodies are neutralizing and over time the function of the enzyme replacement therapy diminishes to the point where the frequency of injection and the dose of the PEG-ADA must be increased. In some cases and for reasons that are not understood, this immune reaction transforms into an autoimmune response. In addition to all the medical difficulties associated with the use of PEG-ADA, the cost of treatment is between $250,000 and $400,000 a year per patient.

ADA-SCID was the first disease in which human gene transfer approach was attempted. None of the three trials conducted in the United States to date have shown promising results, probably due to the fact that they were conducted approximately 10 years ago when the gene transfer technology was not adequate. In the NIH gene transfer trial for ADA-SCID, in which two different vectors were tested, all four participants were maintained on PEG-ADA during the trial. Although results showed no clear immunological or clinical improvement in the participants, a low level of multilineage marking was attained. The concomitant administration of PEG-ADA, that would have prevented the transduced cells from having a selective advantage, may have contributed to the lack of immunological effects.

In a more recent ADA-SCID gene transfer trial in Italy, in which the participants were not receiving concomitant PEG-ADA and using nonmyeloablative conditioning, one participant had a normal number of ADA-producing cells that was maintained 1 year after treatment. A second participant had improvement in clinical values. Preliminary results from these two participants were published in *Science* in June 2002. Regarding restoration of immune function, the first participant's immune function is almost normal, and antibodies with specificity to antigens have developed. The immune function of the second participant is not normal but is significantly higher than before the gene transfer product was administered. After five years, the first participant, who received a large number of transduced cells at a younger age, is well and at home. The third and fourth participants have been administered the gene transfer product, but results about their immune reconstitution are not yet available.

B. Results of a *Jak3* SCID Trial

One research participant has been treated in the JAK3 SCID study. The participant received two infusions of the cells transduced with the gene transfer product and while the research participants did not exhibit immune system reconstitution, no SAEs were observed.

C. RAC Discussion

Dr. Friedmann requested that the RAC again discuss its decision about whether to recommend resumption of non-X-SCID trials.

Dr. P. Johnson suggested that the results in the Italian trial for ADA-SCID suggest evidence of clinical benefit from gene transfer in ADA-SCID.

Dr. Wara noted that the JAK-3 deficiency is more comparable to X-SCID than is ADA-SCID, and it would, therefore, be expected to have a similar risk/benefit ratio.

Dr. DeLuca asked whether other retrovirus clinical trials that target hematopoietic cells had been placed on clinical hold by the FDA. Dr. Rose indicated that, according to the FDA, additional studies have not been placed on hold.

D. Sense of the RAC 2

Dr. Friedmann returned to the two points discussed earlier regarding the non-X-SCID trials and requested that the RAC vote on whether they reflect the sense of the committee.

By a vote of 13 in favor, 2 opposed, and 0 abstentions, the RAC concluded that

- With regard to other SCID gene transfer studies, some participants experienced mild to moderate clinical improvements.

- The NIH RAC finds that resumption of other SCID gene transfer studies is justified contingent upon appropriate informed consent and monitoring plans.

Dr. Rose noted that a portion of the March 2003 RAC meeting may revisit the proceedings regarding this issue.

XI. Day Two Adjournment/Dr. Friedmann

Dr. Friedmann thanked the participants and adjourned the second day of the December 2002 RAC meeting at 6:00 p.m. on December 5, 2002.

XII. Day Three Opening Remarks/Dr. Friedmann

Dr. Friedmann opened the third day of the December 2002 RAC meeting at 8:30 a.m. on December 6, 2002.

XIII. Report From the NIH RAC Informed Consent Working Group/Dr. Lo

Dr. Lo reported that the working group's aim is to provide investigators and IRBs with ideas for improving the informed consent process for gene transfer research and to make the Appendix M requirements more practical. The working group has reviewed the preliminary drafts of a proposed guidance and changes to Appendix M. Another round of internal revisions and suggestions will occur, and a working draft will be provided to all RAC members for comment at a future RAC meeting. Focus groups with research participants and others are planned to obtain feedback about the proposed guidance

A. RAC Discussion

Ms. Kwan suggested that the informed consent working group consider the discussion that occurred on Dec. 5 regarding long-term followup, specimen collection, and monitoring. Dr. Lo agreed that the informed consent working group would take this discussion into account.

XIV. Discussion of Human Gene Transfer Protocol #0208-550: A Phase I/II Study of an Antitumor Vaccination Using Alpha(1,3) Galactosyltransferase (αGal) Expressing Allogeneic Tumor Cells in Patients With Relapsed or Refractory Breast Cancer

Principal Investigator: Roscoe F. Morton, M.D., Stoddard Cancer Research Institute, Iowa Methodist Medical Center

Discussion of Human Gene Transfer Protocol #0210-552: A Phase I/II Study of an Antitumor Vaccination Using αGal Expressing Allogeneic Tumor Cells in Patients With Refractory or Recurrent NSCLC

Principal Investigator: John C. Morris, M.D., NCI/NIH

For both protocols:

Presenter:	Charles J. Link, Jr., M.D., FACP, Stoddard Cancer Research Institute
Sponsor:	New Link Genetics Corporation
RAC Reviewers:	Drs. Gooding, Powers, and Wara
Ad hoc Reviewer:	John Iacomini, Ph.D., Massachusetts General Hospital (via teleconference)

Dr. Friedmann noted that both protocols would be discussed together because they substantially similar; therefore, they were reviewed by the same RAC and ad hoc reviewers. Dr. Link presented a summary of both protocols, then Drs. Morton and Morris commented on each individual protocol. Dr. Link disclosed that he is a principal in New Link Genetics Corporation and has a financial interest in a patent related to these protocols.

A. Summaries of Both Protocols

1. Summary of Protocol #0208-550

Despite the best clinical science and many breakthroughs in biotechnology, the prognosis is not good for women with breast cancer that progresses and spreads beyond the breast. One reason is the cancer becomes resistant to chemotherapy, and resistance to one type of chemotherapy often leads to resistance to other types. In addition, estrogen-dependent breast cancer cells lose their dependency on estrogen and are no longer affected by antihormonal therapies such as tamoxifen. Once the cancer cells spread beyond the breast, treatment options such as surgery are no longer useful.

Data demonstrate that breast cancer cells produce a number of abnormal proteins that are not usually present in the human body. Normally, a woman would develop an immune response that would attack t the abnormal proteins in her cancer. However, for reasons not fully understood, the immune system fails to detect the cancer proteins and, therefore no immune response to the breast cancer cells is mounted. The protocol proposes a new way to make the immune system recognize the cancer cells and encourage an anti-cancer cell response

The protocol's approach combines an unconventional suicide gene effect (direct killing without the need for a prodrug or exogenous co-factors) with an immune enhancement effect (improved tumor antigen presentation). Animals such as mice express sugar molecules on the surfaces of their cells that humans do not produce; therefore, human immune systems quickly recognize cells from "lower" mammals and destroy them. Because of this reaction, it may be possible to inject a mouse gene for these sugars into human cells and have them expressed to stimulate an immune response. The expression of the murine α(1,3) galactosyltransferase (α(1,3)GT) gene results in the cell surface expression of α(1,3) galactose sugars (αgal) on membrane glycoproteins and glycolipids. These sugars are the major target of the human hyperacute rejection response that occurs in xenotransplantation. The α(1,3)GT expressed in human cells renders them susceptible to antibody and complement-mediated cytolysis and results in rapid cell death.

The protocol involves transducing breast cancer cells with the murine gene for the α(1,3) galactosyl sugar. The breast cancer cells would then express the sugar, and hopefully stimulate the immune system. The immune system will also, potentially, recognize the other antigens specific to the breast cancer cell and mount an increased immune response to the cancer. The protocol would be tested in women with breast cancer who have failed at least one salvage therapy.

2. Summary of Protocol #0210-552

Most individuals diagnosed with advanced stage lung cancer will die from the disease. Among the reasons for this, many patients are diagnosed at a time when their lung cancer has already spread to other sites, thus limiting the options for radiation and surgery. In addition, the cancer cells have become resistant to chemotherapy. Scientists have shown that lung cancer cells produce different amounts of

proteins or different types of proteins compared to non-cancerous cells. a number of abnormal numbers and amounts of proteins. For reasons not fully understood, the immune system can fail to detect abnormal cancer proteins.

In a manner comparable to that described for study #550, protocol #552 proposes a new way to make the immune system recognize the cancer and encourage it to attack these cells. Non-small cell lung cancer (NSCLC) cells will be transduced with the murine gene for the α(1,3) galactosyl sugar, and hopefully lead to increased immune response to the specific NSCLC cell antigens.

The protocol would be tested in participants with NSCLC who have failed at least one type of chemotherapy treatment. Participants will be injected with an antitumor vaccine consisting of a mixture of three types of irradiated allogeneic human lung cancer cells that have been transduced with a retroviral vector expressing the (1,3)GT gene.

B. Reviews by RAC Members and Ad Hoc Reviewers

Drs. Gooding, Powers, and Wara and *ad hoc* reviewer Dr. Iacomini submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Gooding's questions dealt primarily with whether a reasonable expectation exists that this procedure will be successful. Additionally, the preclinical data submitted with the protocol did not appear to be relevant to the proposed study. While the data presented during the RAC meeting were pertinent, Dr. Gooding recommended that more surrogate preclinical measures in a more appropriate animal model should be obtained. She suggested that the two clinical trials be conducted sequentially, not simultaneously as proposed. The investigators ultimately need to determine whether the alpha-gal antigen acts as a good adjuvant by augmenting the immune responses to the weaker cancer antigens.

Dr. Powers focused on the investigator's independence and the informed consent process. The protocols should discuss the SAE that occurred in the French X-SCID trial since a retroviral vector is being used. Since participants in both protocols would have to give direct consent, the language about durable power of attorney should be removed from the document. Dr. Powers also suggested that the word treatment be deleted from the informed consent document so as to avoid the therapeutic misconception.

Dr. Powers also recommended that more information about the relationship between the investigators and the sponsoring company should be provided to participants in both protocols. The informed consent documents should be modified to reflect the experience in Phase I when the trial moves to Phase II.

Dr. Iacomini pointed out that although investigators have provided compelling preclinical efficacy data, they have not determined the mechanism of protection, which is a concern because mechanisms leading to tumor rejection could be significantly different in mice and humans. Dr. Iacomini's other concerns and questions included the following: (1) The efficacy data in mice are based on short-term assays; are long-term data available? (2) Are mouse data available that suggest that immunization with allogeneic lines expressing αgal will lead to an antitumor response? (3) Is there a chance that production of αGal-modified proteins in the research participants could induce immunological tolerance to αGal? If so, this possibility should be made clear in the informed consent document. (4) Why have no studies been conducted in nonhuman primates?

Dr. Wara expressed agreement with Drs. Gooding and Iacomini. She suggested that proof of concept and relative absence of risk should be established before trials proceed to Phase II. Moreover, it would be advisable to proceed with only one carefully crafted Phase I trial. Dr. Wara noted that this is an exceedingly interesting hypothesis that, if successful, could be extended as a treatment strategy to numerous other solid tumors. It is possible that preexisting antibodies could be inhibitory; thus, it is not clear that this procedure will work or that there will be no risk. Data from mouse studies do not always mirror clinical experience. In addition, there is a paucity of *in vivo* data to clarify the precise immune response that would elicit tumor lysis.

C. RAC Discussion

The following additional concerns were during the RAC discussion:

- Dr. DeMets raised questions about the proposed dose escalation scheme including: what would happen in the dose-escalation scheme if investigators do not reach the MTD at the highest proposed dose, and how will they know whether an efficacious dose has been reached?
- Dr. Iacomini noted that the level of αgal antibodies in humans could vary dramatically in the population. If such immunity does lead to a priming effect in tumor antigens, how much of a preexisting antibody repertoire would an individual need? What would the pre-existing αgal antibody level need to be to achieve the adjuvant effect?
- Dr. Iacomini asked how this vaccination works in animals with a preexisting tumor, noting that this question is not addressed anywhere in the two proposals.
- Dr. Borror suggested removing the phrase "we believe these vectors are safe" from both informed consent documents. Dose escalation should be well explained in both informed consent documents.

D. Investigator Response

In response to concerns about conducting these trials simultaneously, Dr. Link noted that the products being tested are different: One is a combination of three types of transduced allogeneic lung cancer cells (squamous cell, adenocarcinoma and large cell anaplastic carcinoma cell lines combined), and the other consists of two types of transduced breast cancer cells (an estrogen-responsive and a nonresponsive tumor combined).

Responding to questions about additional mechanistic data, Dr. Link explained that published data on transfection experiments show degrees of protection similar to the degree of protection shown in the irradiated retroviral-transduced vaccine in these two trials. Additional published data show that the αGal-coated tumors are taken up efficiently into macrophages.

Dr. Link responded to suggestions about using a nonhuman primate model before human testing by explaining that the toxicity and antibody response data gathered from the clinical studies using murine vector producer cells that naturally express αGal are informative, and the investigators do not believe that enough additional helpful information would be gained to justify sacrificing primates. Many other types of therapies are tried in humans even when the exact mechanism of action is not known. Investigators have recently received grant support from the Susan G. Komen Foundation and the U.S. Department of Defense to work out the mechanistic issues, but it is anticipated that these experiments will take many years to complete.

Dr. Link agreed to add to the informed consent document information about the chance of αGal-modified polypeptides inducing tolerance to αGal.

Regarding conducting the two trials concurrently, Dr. Link suggested a compromise approach. The second trial would not proceed until 30 days of follow up occurred in the first dose used in the first trial before proceeding with the second protocol.

Dr. Link explained that investigators would attempt to determine the correct dose for efficacy by using some of the secondary end points and the cytokine assays.

In terms of toxicity to the skin, Dr. Link reiterated that injection will be intradermal, not subcutaneous or intravenous. Whole cells will be used.

Dr. Morris explained that the protocols call for an expansion of any dose cohort to six participants if dose-limiting toxicity is seen.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Friedmann noted that there was great enthusiasm for this approach and that it could prove useful in a variety of important solid tumor models. The following recommendations from the RAC were provided to the investigators:

Scientific/Medical Issues

- Due to the potential broad applicability of this new technology to many types of cancer, additional animal studies supporting this approach should be performed.
    - Whether αgal is an appropriate adjuvant to augment the induction of an immune response to tumor antigens is the key question raised by this protocol. A study should be conducted in which allogeneic tumor cells are either transduced with the alpha-gal transgene or not transduced. After injection into alpha-gal knockout mice, the immune response to tumor antigens known to be present on the allogeneic cell line should be compared. This study would be able to answer whether or not the addition of the alpha-gal gene improves the immune response to the tumor antigens.
    - To more closely approximate the proposed clinical study, experiments should be conducted in tumor-bearing alpha-gal gene knockout mice that are immunized to alpha-gal using the dosing schedule proposed in the protocol.
    - Further work to clarify the details of the immune response to the product should be considered.
    - Phase 1 versus phase 2 clinical trials classically require different amounts of preclinical data to proceed and the timing of these recommended additional animal studies should be discussed with the FDA. The animal studies conducted to date focus on the safety of the gene transfer product. Proof-of-concept studies (as recommended above) are generally required prior to initiation of phase 2 clinical trials.
- To enhance safety, the first dose cohort in whichever protocol (i.e., OBA Protocols 0208-550 and 0210-552) is initiated first should be completed and adequately analyzed before initiation of the first dose cohort in the second study.
- In light of the suggestions regarding animal studies, the protocol should be revised to separate the phase 1 and phase 2 components. If this recommendation is not followed and the protocol remains a combined phase 1/2 protocol, then more details regarding the phase 2 component should be provided (such as the primary endpoints, data analysis, reporting timeline for adverse events, etc.)
- A written response to Dr. Iacomini's review should be submitted.

Ethical/Legal/Social Issues

- In regard to the Informed Consent Document:
    - The dose escalation design of the phase 1 studies should be more clearly described.
    - A separate Informed Consent Document for the phase 2 study should be developed and it should contain final outcome information from the phase 1 study.
    - Because the vector used in this study is a retrovirus, more information should be provided about the serious adverse event that occurred in the French X-linked Severe Combined Immunodeficiency Disease trial.
    - All references to "therapy" should be deleted.
    - All statements about the general safety of this approach should be deleted and instead more details regarding potential, albeit rare, adverse events should be provided.

G. Committee Motion 4

It was moved by Dr. Gooding and seconded by Dr. Powers that these recommendations expressed the comments and concerns of the RAC. The vote was 14 in favor, 0 against, and 0 abstentions

XV. Closing Remarks and Adjournment

In response to Ms. Kwan's request, Dr. Rose suggested that the RAC could commend the investigators of the X-SCID trial discussed during this meeting for their expeditious and scientifically sound followup of the SAE, and their openness in sharing that information internationally. She suggested that they exemplify how AEs in gene transfer clinical trials should be handled.

In response to Dr. DeMets' concern, Dr. Friedmann stated that the discussion of the monitoring process will be revisited at the March 2003 RAC meeting. In the interim, language crafted by Dr. Wara regarding how the *NIH Guidelines* might be amended to address enhanced monitoring will be discussed at a future safety symposium on retroviral vectors.

Dr. DeMets requested future discussion about the need for a better data infrastructure.

Dr. Friedmann thanked participants and adjourned the meeting at 10:45 a.m. on December 6, 2002.

[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]

…/S/…

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: …/S/…

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Attachment I
RAC Roster

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Attachment III
Abbreviations and Acronyms

Ad	adenovirus
ADA	adenosine deaminase
AdIV	adenovirus immunotherapeutic vaccine
Ad/L523S	recombinant Ad-5 containing the L523S gene
AE	adverse event
αGal	galactosyltransferase
BRMAC	Biological Response Modifiers Advisory Committee, FDA
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
HGF	human growth factor
HLA	human leukocyte antigen
IHD	ischemic heart disease
IM	intramuscular
IND	investigational new drug
IRB	institutional review board
LAM	linear amplification-mediated
MTD	maximum tolerable dose
NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NSCLC	non-small cell lung cancer
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director
PCR	polymerase chain reaction
PEG-ADA	polyethylene glycol-modified bovine ADA
PI	principal investigator
pVAX/L523S	plasmid DNA containing the L523S gene
RAC	Recombinant DNA Advisory Committee
RCR	replication-competent retrovirus
SAE	serious adverse event
SCID	severe combined immunodeficiency disease
SIN	self-inactivating
VZV	varicella zoster virus
X-SCID	X-chromosome-linked severe combined immunodeficiency disease