RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

February 10, 2003

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

CONTENTS

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

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

Development of T-Cell Acute Lymphoblastic Leukemia (T-ALL) in Two Subjects in a Gene Transfer Clinical Trial for X-SCID

February 10, 2003

The Recombinant DNA Advisory Committee (RAC) was convened for its 89th meeting at 8:30 a.m. on February 10, 2003, at the National Institutes of Health (NIH), Building 31C, Conference Room 6, Bethesda, MD. Dr. Theodore Friedmann (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 5:00 p.m. The following individuals were present for all or part of this meeting.

Committee Members

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

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

Executive Secretary
Stephen M. Rose, OD

***Ad Hoc* Reviewers/Speakers**
Peter D. Aplan, National Cancer Institute (NCI), NIH
Alain Fischer, Hôpital Necker-Enfants Malades (via teleconference)
Dale E. Hammerschmidt, University of Minnesota
David M. Harlan, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, Biological Response Modifiers Advisory Committee, Food and Drug Administration
Carl H. June, University of Pennsylvania
Ilan R. Kirsch, National Cancer Institute, NIH
Warren J. Leonard, National Heart, Lung, and Blood Institute (NHLBI), NIH
Harry Malech, National Institute of Allergy and Infectious Diseases (NIAID), NIH
Gregory H. Reaman, Children's National Medical Center
Naomi Rosenberg, Tufts University School of Medicine

[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.

Daniel R. Salomon, The Scripps Research Institute, Biological Response Modifiers Advisory Committee, Food and Drug Administration
Ricardo U. Sorensen, Louisiana State University
Christof von Kalle, University of Cincinnati/Cincinnati Children's Hospital Research Foundation

Nonvoting Agency/Liaison Representative
Sally L. McCammon, U.S. Department of Health and Human Services

NIH Staff Members
Rima Adler, NHLBI
Richard A. Anderson, National Institute of General Medical Sciences, NIH
Catherine Barnard, OD
Sebastian Brenner, Laboratory of Host Defenses (LHD), Division of Intramural Research, NIAID
Sandra H. Bridges, NIAID
J. Scott Cairns, NIAID
Fabio Candotti, National Human Genome Research Institute (NHGRI), NIH
Sarah Carr, OD
Jan Casadei, NCI
Javier Chinen, NHGRI
Uimook Choi, NIAID
Elaine Collier, National Center for Research Resources (NCRR), NIH
Utpal Dave, NCI
Camilla Day, Center for Scientific Review, NIH
Jordana Deleon, LHD
Suksee Deravin, NIAID
Cindy Dunbar, NHLBI
Kelly T. Fennington, OD
Kagnew Gebreyesus, NIDDK
Suzanne Goodwin, OD
Kailash Gupta, NIAID
Laurie Harris, OD
Beverly Hay, NHGRI
Anthony Hayward, NCRR
Peiman Hematti, NHLBI
Valerie Hurt, Office of the General Counsel, NIH
Robert Jambou, OD
Elizabeth Kang, NIDDK
Richard Knazek, NCRR
Ken Kuramoto, NHLBI
Ching Juh Lai, NIAID
Bob Lanman, OD
André Larochelle, NHLBI
Susan Leibenhaut, FDA
Ke Liu, NCI
Allan Lock, National Institute of Child Health and Human Development, NIH
Sharon A. Mavroukakis, NCI
Cheryl McDonald, OD
R. Rita Misra, NCI
Richard A. Morgan, NCI
Alan Moshell, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
Marina O'Reilly, OD
Roland A. Owens, NIDDK
Alexander Rakowsky, OD
Nicholas Restifo, NCI
Minerva Rojo, Fogarty International Center, NIH
Steven A. Rosenberg, NCI

Gene Rosenthal, OD
Michael Schmidt, National Institute of Dental and Craniofacial Research, NIH
Thomas Shih, OD
Allan Shipp, OD
Lana Skirboll, OD
Danilo A. Tagle, National Institute of Neurological Disorders and Stroke, NIH
Tina Thomas, OD
John Tisdale, NIDDK
Chuck Trimmer, OD
Giselle White, OD
Kouhei Yamashita, LHD

Others
A list of the 157 other attendees appears in Attachment II.

I. Welcome and Opening Remarks: Review of Purpose and Objectives/Drs. Friedmann, Patterson, and Rose

Dr. Friedmann, RAC Chair, called the meeting to order at 8:30 a.m. on February 10, 2003. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on February 5, 2003 (68 FR 5905). The RAC meeting focused on issues surrounding the development of T-cell acute lymphoblastic leukemia (T-ALL) in two research participants in a gene transfer clinical trial for X-linked severe combined immune deficiency (SCID) being conducted in France and the RAC's recommendations as a result of these two events.

Dr. Patterson explained that the NIH convened this special meeting of the RAC to review and discuss a second case of leukemia in a gene transfer clinical trial for X-SCID. The goal of the meeting is to work toward a common understanding of the two events and what they mean for the participants enrolled in this trial and their families, participants in other similar trials, and potential participants contemplating enrollment in future gene transfer trials. On behalf of the Office of Biotechnology Activities (OBA) and the RAC, Dr. Patterson expressed gratitude to Dr. Alain Fischer and his colleagues for their openness in sharing information about the results. Their integrity in this regard has allowed the information to be of benefit not only to participants in their trial but also to all individuals enrolled in similar trials throughout the world. The X-SCID trial has otherwise had very promising outcomes demonstrating efficacy in the children enrolled. Because there have been significant benefits in the trial, it is critically important to reach an understanding of the significance of the adverse events so that the potential risks and the potential benefits of such trials can be determined.

Dr. Friedmann stated that this is a watershed event for the field of human gene transfer: the first-ever combination of a major clinical therapeutic response in a gene transfer study with an obvious treatment-related SAE, a situation indicative of the maturing of the field. He indicated that the RAC's overarching goal is to work through public interactions with investigators to help design scientifically useful studies, to identify potential risks, and to incorporate safeguards to maximize the safety of human gene transfer research. Today's meeting, he noted, is the result of cooperation among groups involved with SCID or similar studies and oversight agencies, all of whom feel an urgent need to determine the mechanisms responsible for the leukemia, to improve the technology, and to devise more effective and safe approaches to future studies. Dr. Friedmann also expressed gratitude to Dr. Fischer and his colleagues for the quality of the studies they have done to understand the events; for the rapid, open, and complete information sharing they undertook; and for their foresight in archiving samples, which has made possible the characterization of this SAE.

II. Case Presentation and Molecular Analyses/Dr. von Kalle (and Dr. Fischer via teleconference)

Dr. von Kalle summarized the characteristics of X-linked SCID as an immunodeficiency caused by a genetic deficiency of the gamma chain that is common to a family of interleukin (IL) receptors. The

deficiency blocks T-cell differentiation, likely at a common lymphoid progenitor or early T-cell progenitor stage, so that patients do not develop functional T-cell or B-cell immunity. Currently, available therapy includes replacement of the immune function with allotransplanted bone marrow, either from a human leukocyte antigen (HLA) identical family donor or from a haploidentical family donor. The success rate of stem-cell transplantation has increased over the years, but there are still significant problems, especially for patients who have existing infections and other serious clinical problems. The option of transplantation is also limited by donor availability.

The gene transfer for X-linked SCID uses a retroviral vector expressing the human common gamma chain (gamma-C) complimentary deoxyribonucleic acid (cDNA), which integrates randomly into chromosomes. Expression of the transgene reconstitutes gamma-C chain expression, which results in the restoration of cell surface expression of a family of interleukin receptors necessary for T cell development. It has been shown in animal models, as well as in the current clinical trial, that gamma-c reconstitution results in functional T cell development, as evidenced by generation of a polyclonal T-cell receptor repertoire. Bone marrow derived stem cells (e.g., CD34+) transduced with the retroviral vectors were reinfused into the participants without any chemotherapy or other conditioning treatment. About 2 to 3 months after reinfusion, T-cell recovery occurred. Because gamma-c expression is required for T cell growth, nearly 100 percent of the T cells in the peripheral blood contained the vector, and there was about one copy of the retroviral vector per cell. The transduced cells had normal functional characteristics, and the thymus showed the presence of recent thymic immigrants (indicating normal thymic function).

From a total of 11 participants in the Paris trial, 9 have experienced immune reconstitution. Most participants in the French trial are young (ranging in age from 1 month to 11 months), many had preexisting infections and other clinical problems symptomatic of immune deficiency, and all exhibited no evidence of endogenous gamma-C activity.

Participant 4 received gene transfer at 1 month of age and showed development of T- and B-cell immune responses including a protective immune response to a varicella-zoster virus (VZV) infection that occurred 30 months after gene transfer. At month 34, an abnormal number of a gamma-delta TCR+ T cell was present, and research participant 4 was considered to have developed an unusual form of acute T-ALL. The research participant has a family history of childhood cancer, which could have been a contributing factor. Research participant 5 received gene transfer at 3 months of age and showed normal T-cell counts up to month 31. However, at month 34, research participant 5 presented with splenomegaly, enlarged mediastinum, and anemia. Further analysis led to a diagnosis of acute T-ALL, but in this case there appeared to be three T cell clones due to the presence of three independent alpha-beta TCR rearrangements.

Molecular analyses by LAM-PCR detected insertion of the vector in the reverse orientation into the first intron of the *LMO-2* gene in research participant 4. In research participant 5, the integration occurred 3 kb upstream of *LMO-2*. The leukemic clones of that participant also showed evidence of a trisomy 10 and a *SIL-TAL* fusion transcript. To calculate the likelihood of insertional activation of *lmo-2* in this type of experiment, Dr. von Kalle considered the size of the human genome (3×10^9 kb) and length of sequence around *LMO-2* that has been observed to activate *LMO-2* by translocation (3×10^4 kb), and estimated that 1 in 100,000 integrations events would randomly occur in the region of activation. Depending on the dose of transduced cells that ranged from 2×10^6 cells to 150×10^6 cells, participants may have received 500-1000 cells with integrations in the region of activation of *LMO-2*. There may be other contributing factors to leukemia such as the effect of the gamma-c transgene on T cell growth and differentiation, clonal seeding efficiency, and immune tolerance.

Insertion site pattern analysis was done for all participants, and five insertions were detected in the *LMO-2* region. A second, non-leukemic clone was found in research participant 4 with the vector inserted 40 kb upstream of *LMO-2*. Two insertions were found in the *LMO-2* region of a third research participant who has no signs of clonal expansion. More than 100 retroviral vector insertion sites have been sequenced from CD34+ stem cells obtained from research participants, but so far, no others have been mapped to regions of the host genome that would raise concern.

Additional investigations are concentrating on the mechanisms of *LMO-2* dysregulation, and analysis of *LMO-2* transcripts, retrospective clone tracing, profile of gene expression in T-ALL clones, mechanisms for screening defects in DNA repair, and additional comprehensive analysis to map all integration sites in CD34+ stem cells from treated research participants.

Drs. Fischer and von Kalle stated that research participants 4 and 5 are both doing well at present, after receiving chemotherapy for the T-ALL.

A. RAC Discussion

Dr. DeLuca asked whether, using archival material, it is possible to know the *LMO-2* transcriptional activity prior to transduction. Dr. von Kalle responded that while *LMO-*2 is not active in mature T cells, *LMO-2* is transcribed in the CD34+ cells that were transduced.

Dr. Salomon noted that research participant 4's insertion was in the reverse transcriptional orientation and asked about the orientation of the vector in the cells of participant 5. Dr. von Kalle explained that the insertion is just upstream of the distal promoter and is in forward transcriptional orientation.

Dr. Kirsch noted that a *SIL-TAL* rearrangement had been discovered in research participant 5 and wondered whether such a rearrangement was found in any other study participants. Dr. Fischer responded that this rearrangement has been found only in the cells of research participant 5 so far; samples are still being analyzed for some of the other participants.

Dr. Noguchi asked whether the researchers believed that preexisting infections in these children might have had a role in causing the SAE. Dr. Fischer indicated that research participants 4 and 5 were the youngest and also the healthiest at the time of gene transfer. Research participant 4 was fully asymptomatic at the age of 1 month, when he was treated, and developed no infections other than chicken pox 3 years later. Research participant 5 had skin lesions related to the presence of maternal T cells, commonly seen in some patients with SCID, but he did not have any identifiable infectious diseases at the time of experimental intervention. All of the other nine research participants did have infections, some of them serious.

Dr. Sorensen asked for a definition of "residual disease" in this case. Dr. Fischer explained that 1 leukemic cell in 1,000, detected in the bone marrow, would probably be considered an indication to perform an allogenic hematopoietic stem-cell transplantation, provided an appropriate donor could be found. If the number of remaining cells carrying the insertion in the *LMO-2* site is much lower in frequency, it will be difficult to determine how to proceed, but the participants will be monitored regularly. Research participant 4 still has some retrovirus transduced T cell with insertions in the LMO-2 site following chemotherapy, but these cells lack the chromosomal translocation seen in the T-ALL cells.

Dr. DeLuca asked how the researchers plan to proceed regarding "participant A" (so designated to maintain this person's confidentiality) who also had insertions in the *LMO-2* region. Dr. Fischer explained that he and his colleagues are monitoring the participants every 3 months even in the absence of clinical symptoms. Included in the monitoring are careful immunological investigations of T-cell phenotype and evaluation of *LMO-2* expression by reverse transcriptase polymerase chain reaction (RT-PCR).

Dr. Friedmann asked about the immunological status of research participants 4 and 5 after chemotherapy. Dr. Fischer responded that research participant 5 only recently received chemotherapy, so no results are known at this time. However, research participant 4 does have gamma-c+ transduced T cells in his blood, and his T-cell counts are similar to those expected in a child with primary leukemia who received chemotherapy treatment. Research participant 4's T-cell reconstitution and his capacity to produce T cells are fairly modest. Dr. Sorensen added that research participant 5, who reports to his clinic, also has T cells, continues to produce immunoglobulins, and is doing well clinically.

B. Comments and Questions from the Public

Dr. Richard P. Junghans, Beth Israel Deaconess Medical Center/Harvard Medical School, asked about the possibility of a secondary event being involved in the development of this SAE. Dr. von Kalle stated that it is unlikely that every insertional event in the proximity of *LMO-2* would induce tumorigenesis because this type of SAE would have been seen earlier and in other research participants. Studies by Dr. Baum showed that over expression of *LMO-2* in transgenic mice was associated with T-cell expansion and eventual development of leukemia in a significant number of animals. Further research, however, is needed to determine the effect of expression promoted by the viral LTR and the effect of gamma-c expression.

III. Pediatric T-ALL/Dr. Reaman

Dr. Reaman provided a synopsis of T-ALL in childhood, in the context of ALL. ALL is the most common pediatric malignancy, representing 25 percent of all cancer diagnoses in individuals younger than 21 years of age. The peak age of incidence is between 2 and 6 years, and more than 3,000 cases are diagnosed per year in the United States, with an incidence rate of 3.7 per 100,000 children. ALL is more common in boys than in girls and in whites than in African Americans.

There are three major classifications for ALL: immunophenotypic, morphologic, and molecular genetic. Immunophenotypic classification defines the cell of origin. B cell precursors account for nearly 85% of childhood ALL while T cell ALL accounts for approximately 15 percent of ALL cases.

Regarding prognostic factors in childhood ALL, the age at time of diagnosis is extremely important in ALL—children younger than 10 years old but older than 1 year old have a much better outcome in response to therapy than do adolescents and young adults. Patients presenting with white counts lower than 10,000 have an extremely favorable prognosis, and individuals with white counts lower than 50,000, currently used as a definition of a standard risk group of children with ALL, have a better outcome in response to therapy than do those with higher white counts. Early response to therapy is defined as either the disappearance of peripheral blood blasts during a 7-day pretreatment with steroids or the presence of less than 5 percent leukemic lymphoblasts in the bone marrow following 1 week of multi-induction chemotherapy. Early response can also be defined by the absence of minimal residual disease after the induction phase of chemotherapy. The other important prognostic factor in childhood ALL is the extent of leukemic burden at the time of diagnosis—children who have mediastinal mass or massive hepatosplenomegaly have a less favorable outcome. Immunophenotype by itself currently is not considered a prognostic factor, taken independently. Cytogenetic nonrandom structural chromosomal abnormalities (e.g., Philadelphia chromosome) are another significant indicator of poor prognosis in childhood ALL; some suggest little chance of survival without hematopoietic stem-cell transplantation.

T-ALL more commonly occurs in males and at age greater than 15 years. Many of these children present with mediastinal mass, hyperleukocytosis, white cell counts exceeding 100,000/mm^3, massive hepatosplenomegaly, an increased incidence of central nervous system (CNS) involvement, and an increased incidence of CNS relapse. While cytogenetic analysis of T-ALL cells has determined that 25% of patients have normal karyotypes, chromosomal deletions or translocations are frequently observed, including a number of translocations involving T cell receptor genes.

Successful treatment of individuals with ALL has greatly improved in recent decades. Currently, 75 percent to 80 percent of children are cured, defined as long-term complete remission off therapy for periods exceeding 5 years. Much of this is the result of the development of risk based specific treatments using prognostic factors such as age, white count, and early response to therapy. Treatment consists of an induction phase involving multiple chemotherapeutic agents, followed by the consolidation phase directed at the CNS, and then maintenance therapy for 2-3 years using antimetabolite based chemotherapy

A. RAC Discussion

Dr. Noguchi suggested that Dr. Reaman's comprehensive review seems to indicate that these two cases of T-ALL are atypical compared to naturally occurring cases of the disease, and he asked what that might

mean for the evaluation of these SAEs. Dr. Reaman responded that, although the clinical presentation of patients 4 and 5 is atypical, the immunophenotype of these individuals is not particularly atypical.

Dr. von Kalle asked Dr. Reaman for advice on how to evaluate minimal residual disease. Dr. Reaman stated that evaluating minimal residual disease in childhood ALL is an area of significant debate within the specialty and that no definitive consensus has been reached. Yet preliminary studies here and in Europe suggest the following definition: presence of more than 1 ALL cell in 100,000 cells using PCR or more than 1 in 10,000 cells using multiparameter flow. The outcome for patients with minimal residual disease is less positive than for those who show no evidence of it.

Dr. Sorensen asked about residual cells with the insertion that are not malignant and how to predict which cell may become proliferative again. Dr. Reaman responded determining which of the remaining residual cells are truly clonogenic and will continue to divide is a main challenge of this field.

B. Public Comment

Joanne C. Delenick requested an estimate of the total number of children that have been placed in remission in all studies in the past 45 years. Dr. Reaman responded that, in the past 10 to 12 years more than 15,000 patients have been treated in multicenter cooperative trials for childhood leukemia.

IV. Retroviruses and Insertional Mutagenesis/Dr. N. Rosenberg

Dr. N. Rosenberg reviewed retroviral integration, and the effects on gene expression. There are four common mechanisms by which insertional mutagenesis occurs with retroviruses: (1) promoter insertion, (2) enhancer insertion, which is the most common mechanism and is orientation and position independent, (3) leader insertion, and (4) terminator insertion. Consequences of insertional activation include upregulation, deregulation, or loss of expression, or altered or truncated gene products.

Changes in gene expression may be quite common as result of retroviral insertion, but most such changes are of no consequence to the cell. More rarely, the cell acquires a selective growth or survival advantage such as when the proviral integration affects expression of genes for transcription factors, chromatin remodeling proteins, growth factors or apoptosis proteins. Assuming that there are 200 proto-oncogenes in a cell and a target size of approximately 1 kilobase, then 1 in 15,000 exposures could result in a tumorigenic event. Model animal systems show that a single integration is usually associated with other changes leading to transformation, but the integration event is the primary rate-limiting step.

While the general consensus in the field is that retroviral integration is largely random, there are conflicting results from different studies. A study of HIV integration by Bushman's group indicated that a disproportionate number of integrations occurred within transcription units, particularly active transcription units. A different study done with an avian retrovirus indicated that nontranscribed regions were preferred. More experimentation is needed to determine whether these differences are due to differences in the viruses or in methods of analysis. In addition to integration, insertional mutagenesis can be affected by other viral factors, such as replication, and LTR sequences that determine tissue specificity and pathogenecity. Host factors, such as genetic background, age, and target cell type also influence tumorigenecity.

Dr. N. Rosenberg noted that integration of the provirus is an inevitable consequence of retrovirus-based gene transfer. Researchers have yet to learn how to target integration and insertional mutagenesis and proto-oncogene activation are likely to occur with high numbers of integrations. To minimize the potential for insertional mutagenesis, Dr. N. Rosenberg suggested keeping the number of transduced cells to the minimum needed, avoiding the use of LTR enhancer and promoter sequences from highly leukemogenic viruses, using a cell-type specific promoter (rather than an LTR), developing better small animal models to test viral vectors, and considering alternative vector designs such as lentivirus-based vectors or inclusion of insulator elements.

A. RAC Discussion

Dr. L. Johnson asked whether there is evidence to show that the use of self-inactivating (SIN) vectors decreases the frequency of tumorigenesis in various models. Dr. N. Rosenberg stated that, where the potential for replication exists, these vectors do decrease tumorigenesis frequency. The SIN modification may be more useful in lentiviral vectors than in vectors derived from MLV since the SIN modification leads to problems generating sufficient vector titer levels.

In response to Dr. Kirsch's question, Dr. N. Rosenberg suggested that the SAEs in the X-SCID study occurred as a result of a random integration followed by selection—expression of a gene in a particularly susceptible cell type.

Dr. Wara asked about the effect of host age at time of infection on integration patterns. Dr. N. Rosenberg described a study done comparing avian retrovirus infection in chick embryos to newborn chicks. The study investigated the integrations found in tumors that arose after the infection. The tumors had integrations into different genes depending whether the infection occurred in embryos or newborn chicks. However, the study did not analyze global integration patterns.

Dr. von Kalle asked whether evidence exists from murine models that a simple nonmultiple hit insertion could integrate into other proto-oncogenes and induce tumorigenesis. While most of the murine studies were done with replicating virus, tumors had been observed to develop under conditions of restricted replication and a single insertion. Dr. N. Rosenberg responded that a single proviral insertion plus other collaborating events is sufficient for tumor development.

Dr. Sidransky (via teleconference) asked whether a small change in the virus would produce a significant change in insertion sites. Dr. N. Rosenberg explained that it would be difficult to predict what minimal changes could be made because not enough is known about how integration is controlled. Although it is clear that the genetic background of the host can have a large effect on insertion, only limited understanding exists about which specific features of that genetic background control these differences.

B. Public Comment

Dr. Cindy Dunbar, NHLBI, pointed out that the word "target" should not be thought of as a target for integration but rather a preferential target that ends up with a tumor.

V. LMO Genes in Leukemogenesis/Dr. Aplan

Dr. Aplan provided background on the closely related *LMO-1* and *LMO-2* genes, which were both initially identified as chromosome translocation breakpoints in T-ALL patients. *LMO-3* and *LMO-4* genes have been identified but are not known to be involved in T-ALL. The *LMO-2* gene is ubiquitously expressed at low levels; *lmo-1* expression is normally restricted to the rhombomere of the hindbrain, pancreatic islet cells, and the testes. Several experiments have shown that *LMO-2* expression is necessary for both embryonic as well as adult hematopoiesis.

Both LMO-1 and LMO-2 encode 158 amino acid proteins that are 58% identical. LMO-2 forms an oligomeric complex containing four other proteins: SCL, LBD, E2A, and GATA1. LMO-2 serves as a bridge in the complex in which E2A/SCL and GATA1 directly contact DNA. E2A is a basic domain, helix-loop-helix (bHLH) transcription factor that binds a specific DNA recognition sequence. The *SCL* gene encodes a basic helix-helix protein that binds both E2A and LMO proteins and is normally expressed primarily in bone marrow and endothelial cells. It is not normally expressed in thymocytes, but more than 60 percent of T-ALL patients express SCL messenger ribonucleic acids. It can be activated either by a chromosome translocation or a site-specific interstitial deletion.

It was first noted that abnormal expression of *LMO-1* and *LMO-2* in thymocytes could be caused by chromosome translocation, although the mechanism by which this occurs is unclear. Mismatch repair

protein deficient mice develop T-cell leukemia, and both *LMO-2* and *SCL* are activated in the leukemic cells. In mouse models of *LMO1/2* translocations, 9-72% of mice develop T-ALL relatively late in life. The incomplete penetrance and late onset suggest cooperating events are required.

One model for LMO leukemogenecity proposes abnormal gene activation induced by the oligomeric complex that contains LMO-2. No target genes have been identified that support this model. The second model proposes a dominant negative mechanism involving sequestration of E-proteins. In an *in vitro* reporter gene assay, E2A was inhibited by SCL and LMO. E2A deficient mice develop T-ALL similar to that seen in LMO-1/SCL mice.

It is possible that *LMO-1* and *LMO-2* genes are interchangeable. They are structurally similar, especially at the LIM domain (named from the Lin-11, Isl-1, and Mec-3 genes) where they are 95 percent identical, and both are leukemogenic when overexpressed in thymus. Currently it is not clear whether searching for *LMO-1* integrations as well as *LMO-2* integrations is important. It is also not clear whether information gleaned from *LMO-1* mouse models will be useful in understanding the leukemogenicity of *LMO-2*.

Because many "leukemic" chromosomal translocations are present in clinically healthy individuals, translocations appear to be are necessary but not sufficient to trigger development of clinical leukemia. Additional mutations are required to produce leukemogenicity. It is not known whether *LMO-2* activating insertions also would require additional mutations.

VI. Defective Cytokine Signaling in X-Linked SCID/Dr. Leonard

Dr. Leonard began by disclosing that he is a co-inventor on two NIH patents, one on the diagnosis and therapy of X-linked SCID and another related to gamma-C knockout mice. X-linked SCID, *jak3*-deficient SCID, and IL-7R deficient SCID are diseases of defective cytokine signaling. Defective IL-7 signaling appears to account for the T cell developmental defect in these disorders. Defective IL-15 signaling is involved in the NK cell defect in X-SCID and JAK-3 SCID, while IL-4 and IL-21 deficiency may be involved with the B cell defect in X-SCID

The gamma chain is common to six cytokine receptors—IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. There are two models for the role of the gamma chain in the receptors. According to one model, the gamma chain confers a commonality to signaling. A second model proposes the opposite role in which the gamma chain might be a mechanism that allows the receptors to compete with each other for a limited common resource. It has not yet been possible to test this model by determining whether the gamma chain is limiting.

Gene transfer studies were done in gamma-C-deficient mice resulting in immune reconstitution with no adverse events; however, the mice were not studied long-term. The key question to consider is whether constitutive expression of the gamma chain predisposes to the development of leukemia. Cells expressing gamma-C should have a growth advantage over cells not expressing gamma-C; however, gamma-C normally is constitutively expressed in T cells and NK cells. It is unknown whether gamma-C levels are limiting, whether the levels of transduced gamma-C are higher than the normal level at any stage of thymocyte development, and whether gamma-c mediated intracellular signaling is constitutively activating JAK kinases or STAT proteins that have been associated with various malignant states.

A. RAC Discussion

Dr. von Kalle asked whether it was possible for the gamma-C expression to become more sensitive and respond to a lower level of stimulation. Dr. Leonard replied that it would be interesting to do a careful dose response study using various cytokines to examine the levels of *jak* kinase phosphorylation and STAT protein phosphorylation in transduced cells compared with similar cells from normal individuals. Such an analysis would indicate whether the sensitivity to cytokines has been enhanced in any way because of the gene transfer.

VII. Points To Consider/Dr. Rose

Dr. Rose introduced the following points to consider in the discussion:

1. Ongoing SCID studies:
   - What additional review should be carried out for ongoing gene transfer studies of x-linked SCID and other types of SCID?
   - How should the assessment of the balance of potential benefits and risks in these protocols be modified in light of our understanding of these two cases?
   - Which protocols should be allowed to proceed?
   - What modifications if any should be made in specific protocols?

2. Ongoing other gene transfer studies using retrovirus vectors:
   - What additional review should be carried out for ongoing gene transfer studies of other conditions involving retrovirus vectors?
   - How should the assessment of the balance of potential benefits and risks in these protocols be modified in light of our understanding of these two cases?
   - What role does the cell type (e.g., hematopoietic cells vs. hematopoietic stem cells) have in the assessment of risks and benefits and recommendations for changes to the ongoing protocol?
   - Which protocols should be allowed to proceed?
   - What modifications if any should be made in specific protocols?

3. New gene transfer studies using retrovirus vectors:
   - What new gene transfer studies involving retrovirus vectors should be allowed to proceed?
   - What role does the choice of cell type (e.g., hematopoietic cells vs. hematopoietic stem cells) have in assessing whether the protocol should be allowed to proceed?
   - What additional review procedures or points to consider, if any, should be instituted?

4. Informed consent:
   - What new information needs to be communicated to participants in ongoing protocols, prospective participants in new protocols, and participants who participated in trials closed to further enrollment and even beyond the protocol defined followup period?

5. How might the risk of leukemia be reduced in gene transfer studies using retrovirus vectors?
   - Should there be screening of potential participants for additional risk factors for leukemia or cancer?
   - Should exclusion criteria be modified?
   - Should there be screening for early detection?

6. Should procedures be instituted for more intensive long-term follow-up or banking of specimens to investigate possible future cases of serious complications?

For each of these questions, policy recommendations would be informed by the following information:
- The nature of the condition being treated, including its seriousness, the availability of alternative therapies, and any predisposition to malignancy
- The nature of the retrovirus vector
- The nature of the gene transferred
- Evidence of clinical benefit from the experimental intervention
- The importance of *in vitro*/*in vivo* clonal selection (i.e., *in vitro*, selection with G418 or other marker, *in vivo*, selection by cell survival)
- Possible interventions—i.e., attempts to eliminate clones with specific integration sites

VIII. FDA Actions in Response to the Second SAE/Philip Noguchi, M.D., U.S. Food and Drug Administration (FDA)

Dr. Noguchi summarized the FDA's actions with regard to the two SAEs in the X-linked SCID clinical trial. As a response to the first event, the FDA identified the investigational new drug studies most similar to the French study, placed three SCID trials on hold, and convened a Biological Response Modifiers Advisory Committee (BRMAC) meeting on October 10, 2002. The BRMAC advised that, because of the great potential benefit, U.S. trials would be allowed to proceed with new safeguards such as revised informed consent documents, notification of institutional review boards (IRBs), and implementation of clinical monitoring plans for early detection of leukemia or leukemia-like symptoms.

Before the U.S. SCID trials had restarted, the FDA was notified of the second SAE. The FDA reexamined all adverse event (AE) information from retroviral trials and found no evidence of vector-caused leukemia. As a precaution, the FDA enlarged the scope of trials placed on clinical hold to include those involving retroviral vector *ex vivo* transduction of hematopoietic stem cells without regard to the disease being treated. As a result, an additional 27 trials were placed on clinical hold. The three SCID trials will continue on hold pending another BRMAC meeting on February 28, 2003.

IX. Public Questions and Comments

Steven A. Rosenberg, NCI

Dr. S. Rosenberg commented that while the FDA clinical hold applied to trials that involved the use of retroviral vectors in hematopoietic stem cells, the NIH recommendations extended to any type of hematopoietic cells. The NIH letter stated that "the NIH is urging investigators conducting retroviral mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available, the possible etiology and risks of these adverse events are considered by the appropriate Federal advisory committees, including the NIH Recombinant DNA Advisory Committee, and recommendations emerge." In response to this recommendation, the NCI IRB elected to defer consideration of a pending protocol involving gene transfer into mature lymphocytes.

Dr. S. Rosenberg described his current immunotherapy research for metastatic melanoma. For the type of patient that would be eligible for the trial, the median survival is less than 1 year with only a 3% survival rate. Dr. S. Rosenberg discussed the clinical responses in one trial in which research participants received adoptive cell transfer of tumor-infiltrating lymphocytes following nonmyeloablative chemotherapy. Because IRBs often consider the recommendations of the RAC to be requirements, Dr. S. Rosenberg urged the RAC to consider the risk/benefit ratio for potential participants with lethal diseases when developing recommendations that send a clear message to the IRBs.

Klaus Cichutek, Ph.D., Chair, Commission for Somatic Gene Therapy, and Chair,* Ad Hoc *Gene Therapy Expert Group, European Agency for the Evaluation of Medicinal Products, Paul-Ehrlich Institut, Langen, Germany (via teleconference)

Dr. Cichutek described the regulatory approach taken in Germany, where there have been 16 trials using retroviral vectors for such indications as chronic granulomatous disease, graft-vs-host disease, cancer, and human immunodeficiency virus (HIV). In response to the report of the first SCID SAE and the detection of leukemia in a mouse model of retroviral gene transfer reported by Dr. Baum's group, the Paul Ehrlich Institute and Commission for Somatic Gene Therapy recommended, in September 2002, a clinical hold on all clinical trials using retrovirally transduced cells.

After the report of the second SAE, a second experts meeting was held February 4, 2003. Ethical and scientific considerations for deciding whether to allow trials to continue include age of participants, disease under investigation, type of modified cells (blood stem cells or others), number of modified cells per dose, average vector copy number per cell, and expected level of *in vivo* cell expansion.

The following decisions were made about specific studies in Germany:

- One trial involving suicide gene transfer into donor lymphocytes has been allowed to continue with modification of the informed consent document.

- The chronic granulomatous disease trial is still on hold; additional discussion of this trial will continue in April 2003.

- The rheumatoid arthritis trial will be allowed to continue pending some protocol changes.

- The HIV trial can continue only with further restrictions of the inclusion criteria.

Richard P. Junghans, M.D., Ph.D., Beth Israel Deaconess Medical Center/Harvard Medical School

Dr. Junghans' research focuses on using retroviral vectors to introduce chimeric T cell receptors into T cells to educate the T cells to attack carcinoembryonic antigen (CEA)-expressing tumors. This work involves mature T cells, which do not live long. The likelihood of leukemia, therefore, is much lower in this type of gene transfer experiment. Patients with CEA-expressing cancers (metastatic breast, lung, and colorectal cancers) do not survive longer than 6 to 12 months. These patients are adults facing death who should be given all the facts and then should given the right to choose whether to become research participants.

Ken Cornetta, M.D., American Society of Gene Therapy (ASGT)

Dr. Cornetta stated that the ASGT has asked its members to review animal and clinical data available on retroviral gene transfer from the past 20 years. The data will be presented in a paper and at a session at the ASGT annual meeting. The Society is also considering recommendations for additional information to be given to research participants to provide context about the prior experience from animal studies and clinical trials. The ASGT called on the FDA and the OBA to harmonize their recommendations whenever possible.

X. Retroviral-Mediated Gene Transfer Into Hematopoietic Cells: Points To Consider/Dr. Friedmann

Dr. Friedmann described the goals of the meeting as trying to understand, as much as currently possible, the mechanisms involved in the SAE and providing recommendations to investigators, IRBs, and institutional biosafety committees (IBCs) about how to proceed in SCID trials and in other trials involving retroviral vectors. As a basis for the discussion, the RAC recommendations from the December 2002 RAC meeting were reviewed.

Dr. Rose reviewed NIH OBA's January 14, 2003, letter to investigators regarding the second SAE in the Paris study which stated in part:

"A second subject in a French trial studying gene transfer as a possible treatment for X-Linked Severe Combined Immunodeficiency has developed a T cell leukemia. As was true in the first event, the second event is directly related to the retroviral mediated insertion of the gene product according to preliminary data presented as described by the investigators.

"The NIH is notifying investigators employing retroviral vectors of the facts currently known about this event since this information is vital to promoting the safe conduct of trials and to ensuring fully informed consent to potential research participants.

"Moreover, the NIH is urging investigators conducting retroviral mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available,

the possible etiology and risks of these adverse events are considered by the appropriate Federal advisory committees, including the NIH Recombinant DNA Advisory Committee, and recommendations emerge."

"Investigators should also know that the FDA has issued a clinical hold for a subset of these trials. Those using retrovirally transduced hematopoietic stem cells."

Dr. Friedmann explained the reasoning behind the difference in wording between the NIH and FDA letters to investigators regarding the second SAE. At the time the letter was written, it had not been determined whether the culprit cell was a CD34+ hematopoietic stem cell. There was concern about any type of cell in the population exposed to the vector. As more is learned about the cellular nature of the event, the recommendations of the RAC may be refined accordingly. Dr. Patterson explained that the letter sent to investigators by the NIH was considered a "placeholder" until this current meeting could be held and more definitive information and recommendations could be provided to investigators.

Dr. Friedmann outlined the draft recommendations for RAC discussion.

1. Retrovirus-based clinical investigators should be urged to confer with their IBCs and IRBs and report to the RAC any modifications or amendments to the protocol, including changes to the informed consent process, stemming from the new X-linked SCID data. Attention should be paid to the following:

- Choice and design of the vector
- *in vivo* tests of survival advantage, and *in vivo* clonal selection of transduced cells
- Additional information about the potential tumorigenicity of the cells based on the nature of the transgene being used
- Methods to minimize the inclusion of cells with potentially undesirable integration sites
- Consideration of incorporating suicide mechanisms into the vector system

2. The NIH should facilitate further research on site-specific recombination, targeted integration, and the *in vivo* selective advantage of transduced cells.

3. The NIH should fund and organize facilities for archiving cell samples.

4. The *NIH Guidelines* Appendix M language should be re-evaluated to require information on transgene function, the selective advantage of transduced cells, plans for sequential sampling and archiving, and updating of the informed consent process.

5. Data sharing should be facilitated between the international gene transfer community and oversight agencies.

A. RAC Discussion

Dr. Lo acknowledged the benefits of the draft recommendations, but he was concerned that recommendations should be developed for the studies currently on clinical hold, which investigators likely would prefer to restart rather than modify significantly. From a human subjects research ethics point of view, there are two key issues: the risk-benefit ratio and informed consent. Recommendations have already been made concerning informed consent, but some consideration should be given to recommendations about how to evaluate the risk in different types of retroviral vector protocols.

Dr. Wara suggested that investigators submit brief amendments that focus on risk-benefit. The RAC would review those amendments in an effort to synthesize a body of knowledge and to advance the field.

Dr. Lo outlined several specific issues to consider in the risk-benefit analysis including the short life expectancy of participants in some trials, the use of target cells that will not have a selective advantage or persist in the body long enough for oncogenesis to occur, and the availability of alternative treatments.

Ms. Kwan encouraged RAC members to exercise caution in wording the recommendations about the risk-benefit ratio. Even for research participants without therapeutic options willing to assume risk, there needs to a reasonable expectation of some benefit, if not directly to the participant, then to future participants or to advance the field.

Dr. Junghans pointed out that benefit to the participant is not a consideration in Phase I clinical trials. The motivation for participants must be that they are contributing to research that likely will not help them, but may help many patients in the future. Phase I trials cannot be given the burden of justifying the treatment of individual patients.

Dr. Hammerschmidt noted that knowledge could be considered a benefit of research. Unreasonable risk cannot be justified merely because a research participant consents to taking that risk. However, if an individual is willing to bear risk for altruistic reasons and researchers believe that the risk is not unreasonable for an individual to bear, proceeding in a clinical trial may be acceptable.

Dr. June expressed concern about the use of stem cells in infants. He voluntarily stopped his HIV clinical trial involving transduction of mature T cells after receiving the RAC letter in January 2003 despite hundreds of patient-years of safety with retrovirally modified T cells without a single case of leukemia. He suggested that the RAC recommendations remain focused on X-linked SCID. Because risk will be case dependent, the RAC should avoid broad language in its recommendations.

Dr. Wara explained that the wording of the NIH letter regarding hematopoietic cells was based upon concerns that the cell population administered in the X-SCID trial contained other types of cells in addition to the CD34+ cells. Dr. von Kalle and Dr. Dunbar responded that the preparations used in the X-SCID study were at least 85 percent to 90 percent CD34+. Because the cells were from participants with X-SCID, the preparation would not have contained any mature T cells.

Dr. P. Johnson suggested focusing the discussion beginning with recommendations for the X-SCID studies. He asked what would happen to the children with X-linked SCID if they had not been treated under Dr. Fischer's protocol. The answer to that question should be the basis on which to make a decision about risk-benefit ratio for this particular population.

Dr. Sorensen suggested that gene transfer can no longer be justified for the treatment of SCID until more is known. Additional *in vitro* experiments should be performed to increase knowledge about insertion sites and secondary events. Because the clinical results were so impressive in Dr. Fischer's study, significant effort should be expended to understand what went wrong. Archiving more cells would be helpful in the future.

Dr. Lo suggested wording as follows: "In reviewing studies currently on hold, the RAC recommends that it would be appropriate for investigators to conclude that studies should be permitted to continue provided that (1) risk may be acceptable because the participant is unlikely to survive long enough for the development of cancer or leukemia mediated by insertional mutagenesis and (2) there is sufficient prospective benefit to balance the risk. Risk may be acceptable because it is expected to be much lower than in the X-linked SCID trial. The transduced cells may have shorter *in vivo* survival and no proliferation or survival advantage. Examples are induction of mature lymphocytes rather than stem cells and synovial cells that would be removed during total knee replacement. The informed consent process adequately informs prospective subjects of the risks and unknowns of insertional mutagenesis. Investigators may want to consider including some mechanisms of ascertaining that participants comprehend this risk."

Dr. Harlan suggested an addition to Dr. Lo's wording to include reference to any other existing therapies and, in this specific instance, that patients with X-linked SCID should not be referred to this kind of clinical trial unless they already had a stem-cell transplant or that one would not be available. Dr. Brody noted that pediatric regulations include specific language that states that inclusion in such clinical trials should be allowed only if there is no alternative therapy with a more favorable risk-benefit ratio. Dr. Simek explained that most studies embrace this kind of wording in their inclusion and exclusion criteria. Dr. von

Kalle stated that while all 11 participants in the X-linked SCID study did not have identical HLA family donors, they did have potential haploidentical donors. However, at the time this gene transfer study began, the data from such transplants were not promising. Haploidentical transplantation has since become more promising for X-linked SCID patients.

Dr. Powers suggested that the RAC discussion refocus on the language crafted by the RAC at its December 2002 meeting regarding X-linked SCID and other SCID clinical trials, including a recommendation covering the concern about other retroviral trials. Suggestions for additional reporting efforts to build the databanks would be a positive addition. Dr. Childress added that the RAC needs to offer some advice about its January 2003 letter to investigators.

Dr. Wara explained that, as a result of this second SAE, it was no longer possible to consider the event as random as was concluded at the December 2002 RAC meeting. Dr. Malech noted that the current data suggests that the leukemia in both participants involves a common mechanism.

Dr. Malech reported that he does not intend to proceed with his X-SCID protocol for 1 or 2 years. Regardless of the outcome of RAC discussions, he would prefer to wait until more is learned about the risks of this type of gene transfer. However, he explained that his concerns were greatest for X-SCID research and did not necessarily extend to other gene transfer protocols.

C. Committee Motion 1

It was moved by Dr. L. Johnson and seconded by Dr. Wara that the RAC recommendations not cover "other" (non-SCID) trials. The vote was 9 in favor, 1 opposed, and 0 abstentions.

XI. RAC Recommendations /Dr. Friedmann

After extensive discussion by RAC members, the following language for RAC recommendations was crafted, based on the wording of the December 2002 RAC meeting recommendations.

"On December 5, 2002 and February 10, 2003, the NIH Recombinant DNA Advisory Committee (RAC) reviewed the clinical and molecular data concerning two adverse events that occurred in a human gene transfer study being conducted in France to correct X-linked SCID. This study involves engraftment of an autologous bone marrow derived, $CD34^+$ hematopoietic stem cell enriched, cell population transduced with a Moloney murine leukemia retrovirus derived replication incompetent vector encoding the common gamma chain (γc) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21. Two children in this study developed T-cell acute lymphoblastic leukemia (T-ALL) almost 3 years after their gene therapy treatment. The leukemias in both children appear to share the common causative mechanism of insertional mutagenesis at or near the *LMO-2* gene with aberrant production of lmo-2 protein, which contributed to the abnormal growth of these leukemic cells. An analysis of the available data from this and other gene transfer clinical trials for SCID led the NIH RAC to conclude that:

- The majority of children in this X-linked SCID gene transfer study have had major clinical improvement to date.

- Of the nine children in this experimental study who had successful engraftment of their gamma-c (γc) transduced cells, two developed leukemia approximately 3 years after treatment and have required chemotherapy; the overall frequency of this adverse event in this trial cannot be determined at this time.

- The gene transfer was a cause of both leukemias.

- The occurrence of leukemia in this protocol is not a random event and constitutes a serious inherent risk in this study.

- Some subjects in gene transfer studies for non X-linked SCID experienced mild to moderate clinical improvement.

These findings led the NIH RAC to make the following recommendations, which will be reviewed and potentially revised as new data become available.

- Pending further data or extenuating circumstances, reviewed on a case-by-case basis, retroviral gene transfer studies for X-linked SCID should be limited to patients who have failed identical or haploidentical stem-cell transplantation or for whom no suitable stem cell donor can be identified. Case-by-case review would include appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

- There are not sufficient data or reports of adverse events directly attributable to the use of retroviral vectors at this time to warrant cessation of other retroviral human gene transfer studies. Including studies for non X-linked SCID. Such studies may be justified contingent upon appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans."

A. Committee Motion 2

It was moved by Dr. L. Johnson and seconded by Dr. Wara that the above wording represents the RAC's current recommendations. The vote was 10 in favor, 0 opposed, and 0 abstentions.

XII. Closing Remarks and Adjournment

Dr. Friedmann thanked participants and adjourned the meeting at 5:00 p.m. on February 10, 2003.

[Note: The RAC recommendations were approved by the NIH Director and have been adopted as NIH policy.]

/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/

Theodore Friedmann, M.D.
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Attachment I
RAC Roster

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Attachment III
Abbreviations and Acronyms

AE	adverse event
ALL	acute lymphoblastic leukemia
ASGT	American Society for Gene Transfer
BRMAC	Biological Response Modifiers Advisory Committee, FDA
cDNA	copy deoxyribonucleic acid
CEA	carcinoembryonic antigen
CNS	central nervous system
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
HIV	human immunodeficiency virus
IBC	institutional biosafety committee
IL	interleukin
IRB	institutional review board
LHD	Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases
LTR	long terminal repeat
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NK	natural killer (cell)
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PCR	polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
SCID	severe combined immunodeficiency disease
T-ALL	T-cell acute lymphoblastic leukemia
VZV	varicella zoster virus
X-SCID	X-chromosome-linked severe combined immunodeficiency disease