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

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

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

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