DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
March 3-4, 1994

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The Recombinant DNA Advisory Committee (RAC) was convened for its fifty-seventh meeting at 9:00 a.m. on March 3, 1994, at the National Institutes of Health (NIH), Building 31, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. LeRoy B. Walters (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee Members:

Ira H. Carmen, University of Illinois
Patricia A. DeLeon, University of Delaware
Roy H. Doi, University of California, Davis
Krishna R. Dronamraju, The Foundation of Human Genetics
Mariann Grossman, Hospital of the University of Pennsylvania
Susan S. Hirano, University of Wisconsin
Arno G. Motulsky, University of Washington
Robertson Parkman, Children's Hospital of Los Angeles
Leonard E. Post, Parke-Davis Pharmaceutical Division
Marian G. Secundy, Howard University College of Medicine
Brian R. Smith, Yale University School of Medicine
Stephen E. Straus, National Institutes of Health
LeRoy B. Walters, Kennedy Institute of Ethics, Georgetown University
Doris T. Zallen, Virginia Polytechnic Institute & State University

Executive Secretary:

Nelson A. Wivel, National Institutes of Health

A committee roster is attached (Attachment I).

National Institutes of Health Staff:

Bobbi Bennett, OD
Christine Boenning, NIAID
Carol Bosken, NHLBI
Sandra Bridges, NIAID
Bruce Bunnell, NCHGR
Sarah Carr, OD
Barry Goldspiel, CC
Betsey Herpin, NIAID

Christine Ireland, OD
Susan Jenks, NCI
H. Clifford Lane, NIAID
Becky Lawson, OD
Martha Lawson, NIAID
Sachiko Kajigaya, NHLBI
Dai Katayose, NCI
Masako Kawase, NHLBI
Catherine McKeon, NIDDK
David Nelson, NCHGR
Prem Seth, NCI
Thomas Shih, OD
Robert Walker, NIAID
Debra Wilson, OD
Jim Yang, NCI

Others:

Paul Aebersold, Food and Drug Administration
W. French Anderson, University of Southern California
Jack Barber, Viagene, Inc.
Bridget Binko, Cell Genesys
Kenneth Brigham, Vanderbilt University
Gracia Buffleben, ACT UP/Golden Gate
Angelo Canonico, Vanderbilt University
Jeff Carey, Genetic Therapy, Inc.
Joy Cavagnaro, Food and Drug Administration
Henry Chang, Shared Medical Research Foundation
Lan Chang, Institute of Biomedical Science
Yawen Chiang, Genetic Therapy, Inc.
Jon Conary, Vanderbilt University
Rathin Das, Miles, Inc.
Mitchell Finer, Cell Genesys
Ralph Freedman, M. D. Anderson Cancer Center
George Gray, Vical, Inc.
Joanna Hales, Cell Genesys
Lowell Harmison, Self-Employed
Evan Hersh, University of Arizona
Morio Hibino, Kennedy Institute of Ethics, Georgetown University
Doug Hickman, T. Rowe Price
Dan Hoth, Cell Genesys
Allen Kamer, The Pink Sheet
Catherine Killion, Baxter Healthcare Corporation
Paul Kleinman, Biopharmaceutical Writers Service
Lori Kobayashi, Hood College
Steven Kradjian, Vical, Inc.
Richard Lazar, Cell Genesys
Timothy Lestingi, University of Chicago
Irene Lowe, Scipress News Bureau
Stephen Lupton, Targeted Genetics Corporation

Tamie Malaska, Targeted Genetics Corporation
Tony Marcel, TMC Development
Michael McCaughan, The Pink Sheet
Brian McGuire, Cell Genesys
Janice McTeague, Genzyme Corporation
Bruce Merchant, Viagene, Inc.
James Merritt, Viagene, Inc.
Andra Miller, Food and Drug Administration
Michael Nash, M. D. Anderson Cancer Center
Jim Neidhart, University of New Mexico
Krista Nowell, Hood College
Sheryl Osborne, Viagene, Inc.
Robert Overell, Targeted Genetics Corporation
Lalida Panpradit, Hood College
Anne Petruska, The Blue Sheet
Lisa Piercey, BioWorld
Stephen Pijar, University of Maryland
Dennis Piszkiewicz, Baxter Healthcare Corporation
Chris Platsoucas, Temple University
Raj Puri, Food and Drug Administration
Urban Ramstedt, Virus Research Institute
Judy Randal, The Economist
Janet Ransom, Organon Teknika Corporation
Paul Recer, Associated Press
Rex Rhein, Biotechnology Newswatch
Margo Roberts, Cell Genesys, Inc.
Joseph Rosenblatt, University of California, Los Angeles
Jack Roth, M. D. Anderson Cancer Center
Patricia Ryan, Genetic Therapy, Inc.
Masahiko Sato, Taisho University
Bruce Schackman, CIT Group
Hans Schreier, Vanderbilt University
Robert Seeger, Children's Hospital of Los Angeles
G. Terry Sharrer, National Museum of American History
Sharon Smith, Hood College
Lisa Song, Hood College
Arlene Stecenko, Vanderbilt University
Margi Stuart, Prevention Research Center
Frank Sturtz, Progenitor, Inc.
Ruth Suchodolski, Genzyme Corporation
Nevin Summers, Ingenex, Inc.
Anthony Taylor, Gene Therapy Advisory Committee Secretariat of the United Kingdom
Larry Thompson, Medical News Network
Paul Tolstoshev, Genetic Therapy, Inc.
Nicholas Vogelzang, University of Chicago
Katharine Whartenby, Food and Drug Administration
Teruhiko Yoshida, National Cancer Center Research Institute
Krisztina Zsebo, Cell Genesys, Inc.

I. CALL TO ORDER

Dr. Walters (Chair) called the meeting to order and stated that the notice of the meeting was published in the *Federal Register* on February 11, 1994 (58 FR 6702), as required by the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. He noted that a quorum was present and outlined the order in which speakers would be recognized. The primary and secondary reviewers will present their comments regarding the proposal, followed by responses from the principal investigators. The Chair will then recognize other committee members, *ad hoc* consultants, other NIH and Federal employees, the public who have submitted written statements prior to the meeting, followed by the public at large.

Dr. Walters requested that the RAC observe a moment of silence in memory of Dr. Brigid Leventhal who died on February 6, 1994. During her service on the RAC, Dr. Leventhal was instrumental in establishing the current process of data management for all RAC approved human gene transfer protocols. Prior to her appointment to the RAC, Dr. Leventhal served on the RAC Human Gene Therapy Subcommittee on which she reviewed the first human gene transfer experiment approved in the United States. Apart from her inexhaustible dedication to the RAC, Dr. Leventhal is recognized for her major contribution to the development of treatments for pediatric leukemia. The RAC is honored to have had the opportunity to interact with a noted physician and patient advocate such as Dr. Leventhal.

Dr. Walters noted several issues previously identified by the RAC, which were followed up by the Office of Recombinant DNA Activities (ORDA). On December 16, 1993, ORDA sent a memorandum to the NIH Office of Legislative Policy Analysis requesting that the language regarding provision of medical care to subjects injured in the course of their participation in clinical research be followed in the proposed health care reform benefits package. ORDA requested immediate notification of any changes to the proposed language by the Administration or Congress.

In a letter dated January 27, 1994, the Institutional Review Board (IRB) of the University of Alabama, Birmingham, Alabama, responded to the RAC's recommendations regarding revisions to the Informed Consent document of Dr. Eric Sorscher (Protocol #9312-066). The IRB noted that in keeping with the institutional policy, the language regarding research related injury will not be modified.

In a letter dated February 3, 1994, the Human Subjects Review Board of the University of California at San Diego, California, deferred to the RAC's recommendation regarding azidothymidine (AZT) administration in human immunodeficiency virus (HIV) seropositive patients (Dr. Flossie Wong-Staal's Protocol #9309-057). AZT will no longer be required as a safeguard against the possible emergence of replication-competent retroviruses (RCR). However, the Board will maintain its requirement for animal toxicity testing for the first 3 lots of transduced cells produced by the investigators.

In a letter dated February 11, 1994, Viagene, Inc., San Diego, California, notified the RAC that suggested revisions to Dr. Richard Haubrich's Informed Consent document (Protocol #9312-062) were incorporated and approved by the IRB of the University of California at San Diego.

No response was received to a December 9, 1993, letter to the IRB of the University of Iowa College of Medicine, Iowa City, Iowa, regarding suggested revisions to Dr. Michael Welsh's Informed Consent document (Protocol #9312-067).

At the request of the NIH Office for the Protection from Research Risk, Dr. Walters will address the Federal Coordinating Council for Science, Engineering and Technology, Human Subjects Review Committee regarding the issue of provision of medical care to patients injured in the course of their participation in biomedical research and compensation for research related injury. Dr. Walters noted that

in 1976 the University of Washington, Seattle, Washington, adopted a self-insurance program for normal volunteers who participate in "non-clinical research." Dr. Parkman inquired whether a Phase I study would be encompassed as "non-clinical research." Dr. Walters responded that subjects injured in a Phase I study would not be covered. There have been a total of 21 claims since 1976 with the largest claim being $6,000. Dr. Walters said that in the United Kingdom, compensation for research related injuries is not a problem since most of the costs are covered by the National Health System. Dr. Walters will provide an update on this issue at the next RAC meeting.

Dr. Parkman remarked that the compensation issue should be addressed in terms of all clinical research not just for human gene therapy. Dr.Wivel added that inclusion of the language in the proposed health care reform benefits package will be followed up through the NIH Office of Legislative Policy Analysis. Dr. Motulsky said that a bipolar system might evolve since the industry sponsored research is more likely to provide the coverage for medical costs of research injuries than research sponsored by the universities. Dr. Walters said that he has noticed a similar trend in the United Kingdom.

II. RAC WORKING GROUP REPORT - DATA MANAGEMENT/DR. SMITH

Dr. Brian Smith, Chair of the RAC Working Group on Data Management, provided a summary of the responses that were submitted by Principal Investigators in response to ORDA's December 27, 1993, request for additional information. He noted that subsequent information provided by the Principal Investigators adequately addressed the concerns of the RAC. However, Dr. Smith noticed a few problems in the data reporting. In his written comments, Dr.Deisseroth (Protocol #9105-007) questioned the RAC's classification of failure to engraft following bone marrow transplant as an adverse effect. Dr. Smith said that failure to engraft should be considered an adverse effect if the frequency of occurrence is not within the statistical range of the expected outcome. Dr. Smith asked whether the RAC has approved the change of vector in Dr. Rosenberg's study (Protocol #9007-003).

Dr. Smith said that responses were not received from either Dr.Cornetta (Protocol #9202-014) or Drs. Galpin and Casciato (Protocol #9306-048). Dr. Parkman said that semi-annual data reporting of any possible adverse events are mandated by the Points to Consider for Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects (Points to Consider).

A motion was made by Dr. Parkman and seconded by Dr. Dronamraju to send follow-up requests for information to Dr. Cornetta and Drs. Galpin and Casciato. If responses are not received by the June 9-10, 1994, RAC meeting, the RAC will reconsider approval of these protocols. The motion passed by a vote of 12 in favor, 1 opposed, and no abstention.

Dr. Walters presented an updated list of approved human gene transfer protocols. The RAC has recommended approval of 67 human gene transfer protocols to date, 59 of these studies have been subsequently approved by the NIH Director, and 8 protocols are contingently approved pending the submission of additional data.

III. DECEMBER 2-3, 1993, RAC MINUTES

The RAC approved a motion made by Dr. Zallen and seconded by Dr. DeLeon to accept the December 2-3, 1993, RAC minutes with the inclusion of minor changes suggested by Drs. Chase, Zallen, and Hirano, by a vote of 13 in favor, 0 opposed, and no abstentions.

IV. CHAIR REPORT ON MINOR MODIFICATIONS TO NIH-APPROVED HUMAN GENE TRANSFER PROTOCOLS/DR. WALTERS

Dr. Walters stated that 11 minor modifications were approved to the following human gene transfer protocols since the December 2-3, 1993, RAC meeting (Attachment II):

DATE	PROTOCOL#	INVESTIGATOR		
1/6/94	9206-023	Cynthia Dunbar		
1/6/94	9206-024	Cynthia Dunbar		
1/6/94	9206-025	Cynthia Dunbar		
2/4/94	9212-034	Ronald Crystal		
2/17/94	9007-003	Steven Rosenberg		
2/17/94	9303-042	Richard Boucher/Michael Knowles		
2/17/94	9312-067	Michael Welsh		
2/25/94	9306-044	Albert Deisseroth		
2/25/94	9306-044	Albert Deisseroth		
9209-027	Friedrich Schuening	I. Call to Order II. RAC Working Group Report - Data Management III. December 2-3, 1993, Recombinant DNA Advisory Committee Minutes IV. Chair Report on Minor Modifications to NIH-Approved Human Gene Transfer Protocols	9209-028	Friedrich Schuening
1/6/94	9206-023	Cynthia Dunbar		
1/6/94	9206-024	Cynthia Dunbar		
1/6/94	9206-025	Cynthia Dunbar		
2/4/94	9212-034	Ronald Crystal		
2/17/94	9007-003	Steven Rosenberg		
2/17/94	9303-042	Richard Boucher/Michael Knowles		
2/17/94	9312-067	Michael Welsh		
2/25/94	9306-044	Albert Deisseroth		
2/25/94	9306-044	Albert Deisseroth		
2/25/94	9209-027	Friedrich Schuening		
2/25/94	9209-028	Friedrich Schuening		

Responding to the question raised by Dr. Smith during his report concerning the vector change in Dr. Rosenberg's study (Protocol #9007-003), Dr. Walters said that the minor modification was approved by the ORDA on February 17, 1994.

V. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* **REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED:** *A PHASE I STUDY OF IMMUNIZATION WITH GAMMA*

Review--Dr. Smith

Dr. Walters called on Dr. Smith to present his primary review of the protocol submitted by Dr. Joseph Rosenblatt of the University of California, Los Angeles, California, and Dr. Robert Seeger of Children's Hospital, Los Angeles, California. Dr. Smith explained that neuroblastoma is the most common extracranial solid tumor in children. Autologous or allogeneic neuroblastoma cell lines will be transduced with the retroviral vector, PHU--IFN, that expresses gamma () interferon. The transduced cells will be lethally irradiated and injected subcutaneously into patients with the objective of inducing an enhanced antitumor response. Both the retroviral vector, pHU--IFN, and the packaging cell line, VCHU, were previously approved by the RAC for Dr. Seigler's melanoma study (Protocol #9306-043). A total of 18 patients under 21 years of age will be divided into two groups: (1) those demonstrating no evidence of disease but who are at significant risk for recurrence or who demonstrate minimal residual disease following the standard chemotherapy and autologous bone marrow transplant regimen; and (2) those who demonstrate persistent or progressive disease. Three dose levels for injections are defined, and 3 patients from each clinical subgroup will be entered at each dose level. A detailed "stop rule" is defined for the trial. The study will characterize safety, toxicity, and clinical antitumor responses. Autologous neuroblastoma cells will be transduced if possible; however, if autologous cells are unavailable, allogeneic cells will be used that have a single human leukocyte antigen (HLA) haplotype match.

Dr. Smith stated that the investigators have provided satisfactory responses to the questions raised in the primary written review of this protocol. The investigators have provided the following subsequent information: (1) data demonstrating that the transduced neuroblastoma cells have been lethally irradiated, (2) data demonstrating that lethally irradiated transduced cells continue to express adequate levels of IFN-, (3) data demonstrating a 50% success rate in establishing primary neuroblastoma cell lines, and (4) data demonstrating efficient transduction of these primary cell lines. Dr. Smith recommended approval of the protocol. Dr. Smith asked the Principal Investigator to comment on the other ongoing melanoma study employing the same retroviral vector (Dr. Seigler's Protocol #9306-043).

Review--Dr. Chase (presented by Dr. Smith)

Dr. Chase's written comments stated that this protocol is similar to other protocols previously approved by the RAC, and the vector and packaging cell line are identical to those approved for Dr. Seigler's study (Protocol #9306-043). Therefore, there are no significant safety issues of concern. Statistical analysis of this study could be improved if the number of treatment groups is reduced and the number of subjects per group is increased. The study should be limited to autologous cells with 3 dose-escalation groups and 6 patients per dose. The investigators responded that the allogeneic group is necessary because autologous cells may be difficult to obtain from all patients and this disease is very rare. The investigators proposed an alternative design involving 2 dose escalation groups: 3 patients in the low dose group and 6 patients in the high dose group. The Informed Consent document does not stipulate that the sponsoring institution will provide compensation for non-negligent injuries arising from participation in the protocol. The assent form language is not understandable to children. Dr. Chase recommended that the term "vaccine" should be deleted from the Informed Consent document since this protocol is a Phase I study.

Review--Ms. Meyers (presented by Dr. Smith)

Ms. Meyers' written comments raised several concerns regarding the Informed Consent document. She reiterated Dr. Chase's comments about the children's assent form, the use of the term "vaccine," and language relating to the provision of medical care if individuals are injured during the course of their

participation in the protocol. An explanation of long-term follow-up was not included. The investigators' written comments noted that the Informed Consent document language is in accordance with the IRB's policy. Since there is the possibility of benefit to subjects, the institution should not have the responsibility of funding treatment for non-negligent complications. Ms. Meyers' written response to the Principal Investigators noted that a Phase I study is not designed to provide benefit to patients.

Other Comments

Dr. Zallen asked about the time frame in which patients receiving allogeneic cells would be informed about their eligibility to participate in the study based on HLA typing. Has HLA typing been completed for all of the cell lines in the cell bank? In regard to the Informed Consent document, the investigators should explain the statement that subjects will be responsible for all costs except for the experimental "vaccine" itself. Dr. Smith added that there is the potential for long-term survival of participants in this study; therefore, long-term care is a pertinent issue.

In response to the RAC's discussion regarding the issue of compensation for research related injuries, Dr. Wivel (Executive Secretary) referred to a letter dated January 28, 1994, from Mr. Robert B. Lanman, NIH Legal Advisor. Mr. Lanman stated that 45 Code of Federal Regulations Section 46.116(a)(6) governs the use of human subjects in research conducted or supported by the Department of Health and Human Services (DHHS). These regulations require that when research involving more than minimal risk is proposed, the subjects of the research must be provided with an explanation as to whether any compensation or any medical treatments are available if injury occurs, what such compensation consists of, and where further information may be obtained. Thus, the RAC's recommendations relating to research-related medical compensation is contrary to the regulations. The institution is required to disclose such policy to any potential participant.

Drs. Parkman and Straus agreed that the RAC should not dwell on this issue during the deliberation of each protocol, citing unfairness to investigators. Dr. Straus stated that although the RAC has the persuasive power to change policy, the committee does not have the legal authority to demand local IRBs to incorporate such changes in their Informed Consent documents.

Investigators' Responses--Drs. Seeger and Rosenblatt

In response to Dr. Zallen's questions about HLA typing, Dr. Seeger responded that 140 cryopreserved tumor cell lines are currently in the process of being HLA typed. From this cell bank, a panel of common HLA types will be identified, e.g., HLA-A2. Approximately 40% of all individuals are HLA-A2 positive. An HLA matched cell line is anticipated for most allogeneic patients. The protocol and the Informed Consent document will be revised to reflect a modified eligibility criterion such that subjects with no available autologous tumor cells will receive a single HLA matched allogeneic cell line. If an HLA matched cell line is unavailable, the subject will be ineligible to participate in the study.

In response to Dr. Zallen's concerns about patient responsibility for research-related costs, Dr. Rosenblatt stated that all of the costs for research will be the responsibility of the institution. Dr. Rosenblatt agreed to revise the assent form in language that is more understandable to children; however, the average age of patients entered on this protocol will be 3 to 4 years old, which is below the age at which a subject can give assent. Most children are diagnosed with neuroblastoma before 7 years of age.

Dr. Walters asked how a determination will be made regarding the assignment of patients to a particular institution. He said that the language regarding compensation for research related injury in the Informed Consent documents differs between the University of California at Los Angeles and Children's Hospital of

Los Angeles. Dr. Seeger responded that most patients will choose the institution where they will receive their care but others will be referred from outside institutions.

Committee Motion

The RAC approved a motion made by Dr. Smith and seconded by Dr. Post to accept the protocol submitted by Dr. Joseph Rosenblatt of the University of California, Los Angeles, California, and Robert Seeger of the Children's Hospital, Los Angeles, California, by a vote of 11 in favor, 1 opposed, and 1 abstention. RAC approval is contingent on the review and approval by the primary RAC reviewers of: (1) a revised protocol that includes an indication of when HLA typing will be performed on subjects considering participation in the allogeneic study, (2) modification of the eligibility criteria to exclude subjects that do not demonstrate a match at any HLA locus, (3) a revised Informed Consent document that includes a statement notifying subjects that they will not continue on this study if an HLA match at any locus is not identified, and (4) a revised patient assent form written in language that is understandable to children.
Dr. Walters noted that Dr. Parkman abstained from voting on this protocol since he is employed by the same institution as Dr. Seeger, the Children's Hospital, Los Angeles, California.

VI. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: ***A PHASE I/II PILOT STUDY OF THE SAFETY OF THE ADOPTIVE TRANSFER OF SYNGENEIC GENE-MODIFIED CYTOTOXIC T-LYMPHOCYTES IN HIV-INFECTED IDENTICAL TWINS*****/DR. WALKER**

Review--Dr. Post

Dr. Walters called on Dr. Post to present his primary review of the protocol submitted by Dr. Robert E. Walker of the NIH, Bethesda, Maryland. Dr. Post said that this protocol is extremely innovative because of the novel function of the transferred gene; T cells will be activated when HIV antigens are encountered. Specifically, in response to the HIV envelope (*env*) protein. HIV infection progressively destroys the human immune system and ultimately results in acquired immunodeficiency syndrome (AIDS). CD8(+) T cells kill virus infected cells. AIDS may result from a break-down of this immune surveillance system. CD8(+) T cells will be obtained from an uninfected identical twin of an HIV-infected patient and transduced with the vector,
r*kat*4SVGF3e-, which contains a hybrid gene that activates the signal transduction system for T cell activation. This hybrid gene includes two components: (1) the extracellular domain of human CD4 (the receptor for the HIV envelope protein), and (2) the intracellular domain of the zeta () chain of the T cell receptor. The transduced T cells will be activated in the presence of HIV envelope proteins without major histocompatibility complex restriction. The genetically modified cells will be purified and expanded to large numbers *in vitro* prior to infusion into the HIV-infected twin. The study is divided into two phases. The first phase involves a single administration of transduced T cells to determine a maximum tolerated safe dose. The second phase involves 6 infusions of this maximum tolerated dose. Subjects will be evaluated for the safety and tolerance of adoptive immunotherapy with the transduced CD8(+) T cells, including monitoring of their immune status, viral burden, clinical symptoms, organ function, and persistence of circulating marked cells. This study will provide baseline information for future studies.

Dr. Post explained that the investigators have adequately responded to the following questions raised in his primary written review: (1) Is there preclinical data that supports this protocol? The investigators subsequently provided a manuscript that describes the preclinical studies. (2) Is there additional information available about this new vector? The investigators responded that the vector, r*kat*4SVGF3e-, was developed to allow high level expression of the transgene following transduction into human T cells.

This vector is similar to the LXSN vector previously approved by the RAC; however, a modification has been introduced at the splice acceptor site which permits expression of the transgene similar to the *env* gene mRNA of the Moloney murine leukemia virus. The investigators have demonstrated high level expression of the hybrid receptor gene in T cells. (3) Will the "ping-pong" method of cocultivation of ecotropic and amphotropic producer clones increase the probability of generating RCR? The investigators have supplied information regarding thorough RCR safety testing. (4) What will happen when large numbers of transduced T cells activated by viral proteins are infused into these HIV(+) patients? The investigators have performed a murine experiment to evaluate this safety issue. A murine tumor cell line was engineered to express the HIV *env* gene, and transplanted in a nude mouse. The mouse was then infused with T cells transduced with the hybrid receptor gene. No serious toxicity was observed in the murine model. Dr. Post cautioned that the solid tumor model is very different from the human situation in which the HIV-infected cells are dispersed throughout the body. This safety issue is significant since the proposed initial cell dose is very high. (5) Will the transduced T cells be susceptible to HIV infection, therefore, expanding the number of HIV-infected cells in the body? The investigators submitted data demonstrating that the transduced cells are at least 1,000-fold less susceptible to viral infection compared to control CD4(+) T cells. Dr. Post suggested that additional data using other clinical HIV isolates is preferable. (6) Will the CD4/ hybrid protein become immunogenic? The investigators responded that no immunological responses have been observed in HIV(+) patients who received large quantities of soluble CD4 proteins. Dr. Post recommended that patients should be monitored for anti-CD4 antibodies.

Review--Dr. Carmen

Dr. Carmen commented that the description of the proposed vector and its derivation are not understandable to laypersons because of the numerous undefined acronyms. He recommended specific changes to the Informed Consent document that would more clearly explain the vector and gene insert. As given, the description conveys little useful information to the research subject.

Review--Dr. Brinckerhoff (presented by Dr. Post)

Dr. Brinckerhoff's written comments raised several concerns. The proposed cell doses, 1 x 108 and 1 x 1010 cells, represent an extremely large number of cells that could result in potential toxicity. How were the initial cell doses determined? The investigators' written response states that the proposed doses are within the range used for other adoptive immunotherapy protocols, e.g., Dr. Rosenberg's (Protocol #9007-003) and Dr. Greenberg's (Protocol #9102-017). Will the hybrid receptor become antigenic? The 7-day experiment demonstrating the lack of transduced T cell infectivity by HIV is inadequate due to the insidious nature of HIV infection, the low level of T cell replication, and a relatively low multiplicity of infection in HIV patients. Is data available from the ongoing 14-day experiment? Efficacy will be difficult to demonstrate since the nature of HIV infection in insidious and variable. The investigators' written response states that the primary endpoint of this study is safety, not efficacy.

Other Comments

Dr. Motulsky asked for additional information regarding the 65 discordant identical twins identified as eligible for this study. This patient population is a valuable resource for other genetic studies. Dr. Parkman inquired about the types and levels of cytokines that are released when the transduced T cells are activated by HIV. Will these cytokines cause adverse effects, e.g., edema, in anatomically defined areas such as the brain? If such a side effect occurs, is therapy available that would alleviate such effects? Is there data demonstrating that steroids cause apoptosis of these clones?

Dr. Zallen inquired whether participation in this study will preclude the 65 discordant twins from participation in future protocols. She recommended that the Informed Consent document be revised to include a statement about long-term follow-up, even if subjects who have received transduced cells terminate their participation in the protocol prematurely. Dr. Hirano asked whether the Phase II portion of this study implies that efficacy is an endpoint.

Dr. Walters called on Ms. Gracia Buffleben of Breast Cancer Action and ACT UP/Golden Gate, to read the written statement submitted by Mr. G'dali Braverman, ACT UP/Golden Gate. Mr. Braverman applauded Cell Genesys (sponsor) for seeking comments on this study from the HIV(+) community. Mr. Braverman's comments focused on scientific issues of the protocol as well as the Informed Consent document. Mr. Braverman suggested the following: (1) potential participants should be informed that participation in this study may exclude their eligibility for other studies, (2) subjects in the control group should be allowed to receive the same treatment as the experimental group once the safety issues have been established, (3) the transduced T cell infectivity experiments should be expanded to include other HIV clinical isolates, (4) lymph node biopsy should be performed, (5) patient eligibility should include females, (6) is the viability of transduced cells affected by freezing and thawing? and (7) patient eligibility should be reduced from 18 to 13 years of age and localized treatment of Kaposi sarcoma should be permitted.

Investigators' Responses--Drs. Walker, Lane, Zsebo, and Roberts

In response to Dr. Carmen's comments about the description of the vector, Dr. Walker agreed to revise these sections of the protocol and the three Informed Consent documents in language that is understandable to laypersons. In response to Dr. Motulsky's question regarding discordant twins, Dr. Walker answered that approximately 10% of the 146 (not 65 as stated earlier) pairs of discordant identical twins enlisted over the last 10 years are female.

Dr. Walker explained that this Phase I/II study is divided into two treatment periods. The first period involves a single infusion of gene modified cells in the experimental group and nonmodified cells in the comparative group. After characterization of toxicities, the second treatment period will involve repeated infusions every 8 weeks for one year. Toxicity, immunological activity, and additional information with regard to activity of the transduced cells will be obtained. Dr. Hirano questioned whether the study design will allow acquisition of statistically significant efficacy data; and if the primary objective is toxicity assessment, why are so many patients needed. Dr. Walker said that according to the suggestion by his consulting statistician, some statistically significant information regarding efficacy may be obtained by increasing the number of patients from 24 to 40 during the second treatment period. There are many identical twins interested in participating in this study; therefore, recruitment is not a serious problem.

Dr. Smith asked about the number of twins who have developed AIDS. Dr. Walker answered that approximately one-third of these subjects have CD4 counts below 200, one-third between 200-500, and one-third above 500.

Dr. Walker responded to the suggestions outlined in Mr. Braverman's written comments. A statement will be included in the Informed Consent document that advises patients that their participation in this protocol may exclude them from other vaccine immunotherapy or gene therapy studies. With regard to the willingness of subjects to participate in the control group of this study, Dr. Walker explained that once the safety issues have been resolved, protocols will be developed to examine efficacy. Patients in the control arm will receive untransduced CD8(+) cells. A companion protocol is in progress that specifically addresses the issue of lymph node biopsy; therefore, subjects will not be excluded from the study if they refuse such biopsies. Tonsil biopsy will be considered for the present study. Dr. Walker did not agree to lower the age of patients from 18 to 13 since this protocol is not a pediatric study. Regarding the question

posed by Dr. Parkman about the management of possible encephalopathy, Dr. Walker responded that an immediate plan has not yet been established for such possible side effects; however, standard medical practices would be implemented.

Dr. Zsebo of Cell Genesys, Inc., Foster City, California, responded to the question on the animal model experiment. Dr. Zsebo said that this experiment was designed to obtain information about efficacy and safety. Two types of experiments have been performed. Tumors were established in nude mice with tumo cells transduced to express the HIV envelope proteins. These tumors were challenged by infusion of mouse T cells transduced with the hybrid CD4 receptor gene. In another experiment, tumor cells and transduced T cells were mixed prior to implantation in nude mice. Notwithstanding the interaction of these two types of cells, no overt inflammatory response was observed. Dr.Zsebo speculated that a probable reason for the negative result might be that not all tumor cells implanted in nude mice weretransduced and expressed HIV envelope proteins, rendering them susceptible to cell killing by T cells transduced with the hybrid receptor. Attempts will be made to purify the tumor cells expressing the HIV envelope proteins before implantation in nude mice in order to repeat these experiments. Dr. Post asked whether there is any evidence to indicate that the transduced T cells, which are present in blood circulation, are activated by the HIV proteins expressed on cells in the tumor mass. Dr.Zsebo conceded that this result is a potential shortcoming of the present model. Some other primate and severe combined immunodeficiency mouse models will be considered, but there is no satisfactory animal model for the present protocol.

Considering the lack of a reliable animal model to assess safety, Dr. Post cautioned that the investigators should proceed with a conservative approach towards this study, i.e., starting at a cell dose of 106 instead of 108 cells with a small number of patients to assess toxicity. Dr. Walker explained that the proposed cell dose of 108 is derived from other studies such as Dr. Greenberg's (Protocol #9202-017). Dr. Post said tha in that study, a consideration has been taken that there is potential difference in toxicity in cytomegalovirus (CMV) vs. HIV infection, and a suicide gene has been incorporated in the study.

Dr. Clifford Lane of NIH, Bethesda, Maryland, responded to Dr. Post's comments that there is a significant difference in CMV and HIV infections but it is technically difficult to incorporate a suicide gene in the present study. Responding to Dr. Parkman's question on side effects, Dr. Lane acknowledged that cortisteroids or other immunosuppressive regimens will be considered as first-line intervention in the event of unforseen side effects. In response to theRAC's concern about committing the valuable discordant twin resource to this study, he explained that a statistically significant sample size is important in order to obtain definitive information for the preliminary assessment of efficacy. This initial information will be used to design future studies that directly address efficacy. Dr.Zallen inquired whether there will be enough eligible patients left for future studies after enrolling the large number of patients in this Phase I/II study. Dr. Lane answered that future studies will be designed usingautologous cells obtained from HIV-infected individuals; therefore, identical twins will be unnecessary. Dr. Smith suggested that perhaps the present trial should be limited to HIV-infected twins with CD4 counts below 200. Dr. Lane said that it is important to assess any immune based therapy with a spectrum of patients since different outcomes may be observed in patients with different immune status. Dr. Lane agreed to decrease the starting dose from x 108 to 1 x 107 cells in response to safety concerns. Dr. Lane described another preliminary animal experiment designed to assess safety. Human peripheral blood lymphocytes were transplanted into severe combined immunodeficiency mice. Human CD4 counts were measured, and no severe destruction of the immune system was observed following infusion of the transduced T cells.

Dr. Margot Roberts of Cell Genesys, Inc., Foster City, California, explained that HIV infectivity of transduced T cell experiments are in progress using a panel of primary HIV isolates and laboratory HIV strains. In addition, other experiments are being performed to assess the antiviral activity of the

transduced T cells. Antiviral activity of T cells expressing the CD4/ hybrid receptor has been observed toward cells infected with the strain IIIB of HIV-1. Dr. Parkman inquired about the cytokine profile of the activated T cells. Dr. Roberts explained that the profile of CD4/ hybrid receptor activation is similar to activation by the normal T cell receptor, e.g., low levels of gamma-interferon (IFN), -IFN, granulocyte colony stimulating factor (G-CSF), tumor necrosis factor (TNF)-, TNF-, and IL-4. Dr. Parkman noted that toxicity is often associated with certain cytokines, e.g., TNF. Dr. Straus asked whether all or only a small fraction of the transduced T cells when infused into patients will be responsive to HIV antigen stimulation. Dr. Roberts said that the cytolytic activity is specific; only cells expressing the HIV envelope are killed by the transduced T cells. Dr. Straus expressed his concern about the possible systematic effects of cytokines that may be released when large numbers of transduced T cells activated by HIV in the blood circulation. The amount of cytokine release may be comparable, whether it was triggered through the T cell receptor or the CD4- chimeric receptor.

Dr. Roberts alluded to studies demonstrating that only those cells expressing HIV envelope antigens were killed by activated T cells. The addition of "innocent" cells indicated that they were not targets for lysis. Thus, it was concluded that it was unlikely that there would be problems associated with nonspecific activity. The use of dose escalation studies in patients will allow for careful monitoring of responses.

Dr. Parkman noted the importance of quantitating cytokine release in order to determine a valid starting dose. Dr. Post suggested that the RAC approve a preliminary study on a small group of patients at a starting cell dose of 1 x 107 transduced T cells in order to assess toxicity. If 1 x 107 cells is determined to be a safe dose, the investigators could proceed with the dose-escalation study as originally proposed. Dr. Parkman suggested that the RAC should require submission of quantitative cytokine release data as a stipulation for approval in order to properly assess an adequate cell starting dose. Dr. Parkman suggested quantitating the cytokines released by 1 x 107 activated cells. Dr. Straus suggested that patients should be monitored for circulating plasma cytokine levels following cell infusion.

Committee Motion

The RAC approved a motion made by Dr. Post and seconded by Dr. Smith to accept the protocol submitted by Dr. Robert Walker of the NIH, Bethesda, Maryland, by a vote of 12 in favor, 0 opposed, and 1 abstention. RAC approval of the protocol is contingent on review and approval of the following by the primary reviewers: (1) a revised experimental design that includes a treatment group that will receive a single administration of 1 x 107 HIV-specific CD8(+) cells (the number of subjects to be determined by the investigator) in addition to the 40 patients who will receive multiple doses of between 1 x 108 and 1 x 1010 cells; (2) inclusion of a statement in the protocol that addresses possible treatments available in the event of unforseen toxicity, e.g., encephalitis; (3) data demonstrating that expression of the universal receptor in a panel of primary clinical isolates obtained from HIV(+) individuals does not increase the susceptibility of these cells to HIV infection and data derived from ongoing 14-day experiments involving cell proliferation versus viral replication; (4) quantitative data derived from *in vitro* experiments demonstrating the amount of cytokine(s) produced/1 x 107 cells/24 hours; (5) inclusion of a statement in the protocol which describes the addition of anti-CD4 antibody monitoring; and (6) a revised Informed Consent document incorporating modifications submitted by Dr. Carmen and "in the spirit of" Mr.G'dali Braverman's comments.

Dr. Walters noted that Dr. Straus abstained from voting on this protocol since he is employed by the same institution as Dr. Walker, NIH.

VII. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: *EXPRESSION OF AN EXOGENOUSLY ADMINISTERED*

Review--Dr. Parkman

Dr. Walters called on Dr. Parkman to present his primary review of the protocol submitted by Dr. Kenneth L. Brigham of Vanderbilt University, Nashville, Tennessee. Dr. Parkman stated that the alpha-1-antitrypsin (AAT) protein is produced by normal lung cells to neutralize the damaging proteolytic enzymes. Two clinical settings are proposed for this study: (1) patients who have inherited a congenital defect which prohibits AAT production, and (2) patients with adult respiratory distress syndrome. Patients who inherit a defective AAT gene develop emphysema at an early age. Patients with adult respiration distress syndrome release large amounts of digestive enzymes that can overwhelm the protective effect of AAT as a result of infection, trauma, etc. The basis of this proposal is that lung cells may be protected from the damaging effects of excessive levels of digestive enzymes, whether from an inherited deficiency or as a result of acute damage, by genetically modifying these cells to produce increased levels of AAT. The investigators propose to transfer the AAT gene into the nasal and lower airway cells using a plasmid DNA/liposome delivery system. The non-viral plasmid DNA construct, pCMV4-AAT, consists of promoters, enhancers, and RNA processing sites for the expression of human AAT. Individuals with congenital AAT deficiency will be monitored for local AAT expression following administration of pCMV4-AAT to the nasal mucosa. Patients scheduled for partial or total lung resection for cancer within 2 or 3 days will be monitored for the presence and expression of pCMB4-AAT in resected lung tissue.

Dr. Parkman explained that the gene delivery approach is very similar to the methods used for the cystic fibrosis protocols that were previously approved by the RAC. However, the investigators have submitted insufficient data demonstrating transduction efficiency and adequate expression of the AAT gene. Transduction efficiency was successfully demonstrated in the cystic fibrosis protocols by visualization of the blue color which resulted from the transduction of the reporter gene, galactosidase, on the surface of the trachea and lung. Although the investigators have provided immunohistochemical data on cross sections of lung tissue for the current proposal, it is difficult to estimate the percentage of epithelial cells that express the AAT gene. The investigators' written response to Dr. Parkman's concerns state that in contrast to the cystic fibrosis transmembrane conductance regulator protein, AAT is a secreted protein; therefore, the efficacy of gene transfer will depend more on the localization and quantity of protein expressed than on the fraction of cells transfected. Dr. Parkman reiterated his predilection regarding demonstration of efficient transduction and its importance for this *in vivo* gene transfer experiment. A preferable method would be to stain for the expression of the transgene in the mucosal surface of a resected bronchus to estimate the percentage of transduced epithelial cells. As compared with previously approved cystic fibrosis protocols, the preclinical animal studies of the present protocol are inadequate. Dr. Parkman recommended that the investigators should be required to provide additional data demonstrating the frequency of transduction in both bronchial and nasal mucosal cells in a preclinical animal model.

Review--Dr. Miller (presented by Dr. Parkman)

Dr. Miller's written comments stated that this protocol employs a non-viral plasmid DNA vector which does not pose any significant risk from a recombinant DNA aspect. The Biosafety Level (BL) 2 containment, which was recommended by the Institutional Biosafety Committee for the animal studies, is overly stringent and should be reduced to BL1 containment. The key issue with regard to clinical application is the level of AAT production. Normal individuals express very high endogenous levels of AAT and AAT deficient individuals express low levels of AAT; therefore, expression of the AAT transgene may not be distinguishable from endogenous levels. While the investigators can conduct *in situ* vector RNA analysis, pathology studies, etc., quantitative data about vector-encoded AAT expression may be elusive. Dr. Miller

suggested that the nasal mucosa experiment should be performed in large animals rather than in humans

Review--Dr. Zallen

Dr. Zallen raised several concerns about the experimental design of this study in terms of risks and benefits, the informed consent process, and Informed Consent document. In her written review, DrZallen questioned why tissues will be examined 72 hours after vector administration in the proposed human study, but the preclinical animal studies were conducted at 24 hours. Why were the animal experiments not extended to 72 hours to obtain comparable data? In their written response, the investigators stated that the protocol would be modified for the human experiment to include tissue examination between 24 and 48 hours following vector administration. How many patients will be entered onto the study? In their written response, the investigators stated that 5 patients will be entered on the bronchial instillation protocol and 6 patients will be entered on the nasal instillation protocol. Dr. Zallen expressed concern about possible conflict of interest as a result of investigators obtaining informed consent from their own patients. Under such circumstances, patients could feel obligated to participate in this study. A third party should be involved in the informed consent process. The investigators should elaborate on their comments regarding the lack of necessity for long-term follow-up. She noted Ms. Meyers' written comments about the failure to include information about alternative enzyme replacement (prolastin therapy) in the Informed Consent document.

Other Comments

Ms. Grossman agreed with Drs. Parkman and Millers' recommendations about the necessity for additional preclinical data derived from an appropriate animal model. Dr. DeLeon asked how expression of the transgene will be distinguished from endogenous AAT expression. Dr. Parkman explained that the investigators will conduct *in situ* RNA analysis to distinguish endogenous versus transgene expression.

Investigator Response--Dr. Brigham

Dr. Brigham responded to the questions concerning transduction efficiency and *in vivo* expression of the transgene in preclinical studies. He presented data demonstrating histochemical staining of the entire airway epithelium of rabbits with an AAT antibody following aerosol delivery of the DNA/liposome complex. Dr. Parkman commented that although transgene expression is demonstrated in cross sections obtained from airway tissue, a three-dimensional analysis is preferable. Dr. Brigham expressed his reservations about using the -galactosidase reporter gene to demonstrate transgene expression in the surface of bronchial epithelium, citing the possibility of obtaining false positive results. Serial cross sections will reveal expression in a three-dimensional sense. Dr. Brigham noted that *in vitro* and *in vivo* experiments have been published indicating that 10 to 15% of cells express the AAT protein. Dr. Parkman noted that the RAC has not had the opportunity to review this data and recommended that such data should be submitted as a stipulation for approval. Dr. Brigham agreed to submit the requested data with the reporter gene. Dr. Brigham presented *in vitro* data demonstrating protection against protease digestion of bronchial epithelial cells by the AAT transgene. Detection of transgene expression in normal individuals is complicated by the fact that normal lungs have high levels of endogenous AAT activity. Since the lungs are not the normal source of AAT synthesis (the protein is made in the liver and transported to the lungs), it is possible to demonstrate *de novo* synthesis of AAT by the transgene in organ cultures of the lung. The DNA/liposome complex will be instilled via bronchoscope to a distal wedge of the lung. Following resection, the tissue will be examined by serial cross sections to detect *in vivo* transgene expression. Histological toxicity data will be obtained regarding inflammatory responses.

Dr. Parkman reviewed the published protein expression data described previously by Dr. Brigham.

Following bronchial administration, approximately one-third of the rabbit epithelial cells express the human AAT protein as demonstrated by fluorescence labelling. The transgene was detected in the liver of rabbits 90 minutes following aerosol administration of DNA/liposome complex to the lungs. Such data raises questions about the possibility of germ-line integration and the necessity of long-term follow-up since some of the AAT deficient patients will have long life spans.

Dr. Brigham said that systemic distribution of vector DNA is a legitimate concern; however, the rabbit experiments involved aerosol delivery to the entire lungs and not the localized delivery proposed for the human protocol. Vector DNA was not detected in either the ovaries or testes of animals via intravenous delivery of DNA/liposome complexes; therefore, germ-line transmission is not a concern. Dr. Parkman suggested inclusion of a statement in the Informed Consent document about the possibility of low level systemic absorption. Dr. Brigham agreed to include such a statement.

In response to the issues raised by Dr. Zallen, Dr. Brigham stated that: (1) the experimental period for the human study will be reduced from 72 to 48 hours, (2) the investigators will not obtain informed consent from their own patients, and (3) statements will be included in the Informed Consent document regarding long-term patient follow-up and a request for autopsy. Dr. Parkman explained that due to the experimental nature of gene transfer at present, these requirements are appropriate. Responding to Ms. Meyers' concern about alternative prolastin therapy, Dr. Brigham explained that the majority of patients that enter the study will be receive enzyme replacement therapy. Prolastin will be discontinued only for a period of 1 month during the gene transfer experiment. A 1 month interruption in prolastin therapy will not significantly affect the course of the patients' disease. Dr. Brigham agreed to amend the statement in the Informed Consent document regarding provision of medical care in the event of research-related injury.

Dr. Brigham expressed his opinion regarding the adequacy of the preclinical studies and their pertinence to the human study. He emphasized that extensive expression of the transgene was demonstrated using the same vector proposed for the human study. This AAT protocol differs from the cystic fibrosis studies in several important aspects, i.e., AAT is a secreted protein that functions in small airways and peripheral alveoli of the lungs; therefore, the animal experiments were designed to demonstrate transgene expression in these areas rather than in trachea and large bronchi as was demonstrated for the cystic fibrosis protocols. The liposome delivery method is not novel and has been approved by the RAC for several other protocols.

Committee Motion

A motion was made by Dr. Parkman and seconded by Dr. Secundy to approve the protocol contingent on the review and approval of the following by the primary reviewers: (1) transduction efficiency data demonstrating a rate of 10-15% transduction *in situ*, and (2) a revised Informed Consent document that includes statements describing the possibility of systemic absorption of vector DNA, the necessity for long term follow-up, and a request for autopsy. The motion for approval passed by a vote of 12 in favor, 0 opposed, and 1 abstention.

Dr. Post abstained from voting due to a conflict of interest (collaborates with Dr. Leaf Huang, a co-investigator on this study).

VIII. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: *USE OF A RETROVIRAL VECTOR TO STUDY THE TRAFFICKING PATTERNS OF PURIFIED OVARIAN TUMOR INFILTRATING LYMPHOCYTES (TIL) USED IN INTRAPERITONEAL ADOPTIVE IMMUNOTHERAPY OF OVARIAN CANCER PATIENTS - A PILOT STUDY*/**DR. FREEDMAN**

Review--Dr. Brinckerhoff (presented by Dr. Dronamraju)

Dr. Walters called on Dr. Dronamraju to summarize Dr. Brinckerhoff's written primary review of the protocol submitted by Dr. Ralph Freedman of MD Anderson Cancer Center, Houston, Texas. This protocol is a resubmission of the proposal that was deferred by the RAC at its June 7-8, 1993, meeting. The RAC deferred the original proposal based on the following: (1) inadequate data demonstrating efficient TIL transduction; (2) insufficient data demonstrating selectivity, i.e., specific trafficking of TIL to tumor sites; (3) incomplete statistical analysis; (4) the Informed Consent document must be revised in simplified language; and (5) concerns about patient responsibility for research-related costs must be addressed. The goal of this protocol is to develop TILs that can be adoptively transferred for the treatment of ovarian carcinoma.

Following intraperitoneal administration of neoR marked TIL, ovarian cancer patients will be monitored for specific migration of TIL to the site of the tumor. The peritoneal fluid and peripheral blood of these patients will be monitored for neoR and the number of CD8(+) cells will be quantitated at 24 hours, 7 days, and 18 days. The investigators are capable of detecting 1 in 100,000 cells by polymerase chain reaction (PCR) analysis. The preclinical data demonstrated that ovarian TIL, which were expanded in low dose interleukin-2 (IL-2), were CD3(+) and CD8(+) and exhibited preferential killing of autologous ovarian tumor cells. A preliminary study involving TIL and IL-2 administration to patients with advanced refractory ovarian carcinoma demonstrated an increase in radioactive uptake in patients' liver metastases. In this resubmission, the investigators have provided marginal data demonstrating their ability to detect 1 in 100,000 neoR marked TIL. In Dr. Brinckerhoff's written comments, she states that the protocol is poorly written and the rationale for the study is poorly stated. Why has the proposed number of patients been reduced from 20 to 10? How will these patients be selected? The investigators' written response to Dr. Brinckerhoff's comments state that they are able to obtain 10 to 12% transduction efficiency; however, supporting data was not submitted. Most of the issues raised by Dr. Brinckerhoff remain outstanding.

Review--Dr. Dronamraju

Dr. Dronamraju raised several issues that must be addressed by the investigators: (1) the statement in the Informed Consent document that explains that the patient cannot be reimbursed for any costs associated with research related injuries, (2) the transduction efficiency must be supported by adequate data, (3) data must be submitted demonstrating that TIL trafficking can be distinguished between tumor and adjacent normal tissues by PCR, and (4) the investigator's statement regarding lack of necessity in determining whether transgene expression should be clarified.

Review--Dr. Secundy

Dr. Secundy commented that the Informed Consent document was not written in language understandable to laypersons. There is no clear description of the experiments that will be performed, and there are several inconsistences between the Informed Consent document and the protocol, e.g., possible side effects.

Dr. Secundy summarized the written comments submitted by Ms. Meyers. The Informed Consent document language should be simplified. Patients should not be required to cover any costs related to research.

Other Comments

Dr. Parkman explained that the 10 to 12% transduction rate noted by the investigators refers to experiments conducted with cell lines rather than primary cultures; therefore, these results probably do no translate to the clinical setting. The investigators must address whether transduction affects the cytolytic activity of T lymphocytes. Tumor-specific trafficking of neoR marked T cells should be compared to surrounding normal tissue that has a blood supply comparable to the tumor. The marker gene may persist longer in blood cells than in tumor cells.

Dr. Post stated that the protocol is very confusing and asked the investigators to provide a clear description of all clinical and experimental procedures.

Dr. Zallen agreed with Dr. Secundy's assessment that the Informed Consent document is written in language that is not understandable to laypersons. Dr. Zallen stated that the section explaining that patients will be responsible for some of the research costs is unacceptable. The investigators should provide a detailed description of the informed consent process.

Investigator Response--Dr. Freedman

As a point of clarification, Dr. Freedman stated that two separate protocols and Informed Consent documents were submitted, one for the ongoing TIL protocol and the other for the gene marking study. No patient will be entered onto the gene marking study unless he/she has previously been entered onto the TIL study. The objective of the gene marking study is to determine whether neoR marked TIL can be detected at the tumor site 3 months following TIL administration. Three months after infusion of TIL cells, samples will be obtained by laparoscopy. A total of 10 patients will receive neoR marked TIL. Dr. Parkman noted the neoR gene was not detectable in melanoma patients 3 months post-infusion in Dr. Rosenberg's RAC-approved protocol. Dr. Parkman expressed his concern about the proposed experimental design. The investigators propose a single 90 day time point to detect neoR marked TIL. Dr. Freedman responded that this 3 month period is dictated by the ongoing TIL protocol because this time point is the optimal time period to examine the therapeutic effects of TIL. Patients should not be required to undergo an additional laparoscopy in order to obtain tissue samples. This study would be very difficult to redesign. Dr. Smith inquired about the number of patients that will be evaluable at 3 months. Dr. Freedman answered that approximately 75% of the patients should be evaluable.

Dr. Parkman expressed his concern that there is no study indicating that the marked TIL cells are detectable 90 days post-infusion. There may be no useful information to be obtained by examining the TIL cells at a single time point in the present study design. Dr. Parkman said that a shorter time point such as 30 days appears to be preferable.

Dr. Parkman said that most of the marked TIL cells will be in the blood circulation; therefore, blood supply of the tissue samples will be critically important. TIL activity should be compared by biopsy of the omentum versus normal peritoneal tissue since the amount of blood supply will vary at different locations.

Dr. Freedman presented data demonstrating the level of sensitivity of the PCR assay. PCR analysis detects 1 in 100,000 neoR marked cells. Dr. Smith expressed his concern whether 10 patients would yield statistically significant information. Dr. Parkman explained that normal peritoneal tissue obtained by laparoscopy may not represent the best tissue for comparison since the blood supply is significantly different than that of the tumor.

Dr. Chris Platsoucas of Temple University responded to questions about transduction efficiency. The 10 to 12% transduction efficiency data refers to primary TIL cells rather than to cultured cell lines. With regard to transgene expression, Dr. Freedman explained that this protocol is a marking study; therefore,

expression is of secondary interest.

Dr. Freedman responded to concerns about patient responsibility for some of the research costs. This statement in question was required by the MD Anderson Cancer Center's IRB and its legal counsel. Dr. Secundy asked whether such a statement is required for all MD Anderson Cancer Center protocols. Dr. Walters noted that this statement was not included in other MD Anderson Cancer Center gene marking protocols previously reviewed by the RAC.

Dr. Post asked about the experimental design of this study. The schema combined treatment flow charts of an ongoing TIL therapy protocol with the present gene marking study. Drs. Post, Smith, Parkman, and Straus asked many questions in order to clarify how patients will be infused with the marked TIL cells and how samples will be obtained and analyzed. Drs. Freedman and Platsoucas attempted to clarify the uncertainty about the treatment schema. Dr. Motulsky recommended that the investigators submit a revised protocol incorporating all of the suggestions referred by the RAC. Dr. Parkman said that the revised protocol should include a scientific rationale that supports tissue sampling 90 days post-infusion. Do the neoR sequences persist at 90 days?

Dr. Secundy recommended that a revised Informed Consent document should be required that includes a clear rationale as to the purpose and schedule for all clinical procedures and a description of any possible risks and side effects of these procedures.

Committee Motion

A motion was made by Dr. Motulsky and seconded by Ms. Grossman to defer approval of the protocol until the investigators return to the full RAC with the following: (1) a modified protocol that includes a revised treatment schema, and (2) a revised Informed Consent document that describes the clinical procedures to be performed in language that is understandable to laypersons. The motion to defer the protocol passed by a vote of 12 in favor, 1 opposed, and no abstentions.

IX. IX. REPORT FROM THE RAC WORKING GROUP ON VACCINES--AMENDMENTS TO FOOTNOTE 21 OF THE *NIH GUIDELINES* REGARDING THE DEFINITION OF RECOMBINANT DNA VACCINES/DR. POST

Dr. Walters called on Dr. Post, Chair of the RAC Working Group on Vaccines, to provide background information regarding the proposed amendment to Footnote 21 of the *NIH Guidelines*. Dr. Post explained that the current Footnote 21, which defines experiments involving the administration of recombinant DNA to human subjects that are exempt from the *NIH Guidelines*, was adopted in 1986. The original definition of Footnote 21 is outdated due to the scientific advances in recombinant DNA technology. The Working Group on Vaccines (Drs. Post, Parkman, and Straus) was established to formulate a revised definition of Footnote 21. The amended version of Footnote 21 (Version A) reads:

Version A: "Experiments where the induction or enhancement of an immune response to a vector-encoded immunogen is the major therapeutic goal, and such an immune response has been demonstrated in model systems, are not covered under Section III-A-4 of the Guidelines. Such experiments can occur without RAC review if a Federal regulatory agency has approved the experiments."

The proposed definition emphasizes the immune response to a "vector-encoded immunogen;" therefore, other cellular immunogens would be excluded, e.g., genetically modified cells expressing IL-2 and cells modified to express a histocompatibility antigen. The proposed definition is intended to include

immunogens encoded by vectors derived from vaccinia viruses, adenoviruses, and retroviruses.

Drs. Parkman and Straus proposed an alternative definition (Version B) for Footnote 21.

Version B: "Human studies in which the induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in a model system, and the persistence of the vector-encoded immunogen is not expected, are not covered under Section III-A-4 of the *NIH Guidelines*. Such studies can be initiated without RAC review if approved by another Federal regulatory agency."

Dr. Post suggested that the term "persistence" should be removed from Version B since persistence is difficult to define, e.g., adenovirus and retrovirus vectors have been shown to persist to some extent in humans.

Dr. Parkman explained that for the purposes of Footnote 21, "persistence" is defined as whether the construct is intended to be expressed for a significant period of time in order to achieve prolonged stimulation that elicits an immune response. The investigator's intent regarding persistent expression supersedes any residual biochemical persistence. One example of an exempt vaccine covered by Version B would be a retrovirus construct encoding an HIV antigen that is not intended to persist. Although there may be biochemical persistence, the experiment is considered exempt from the *NIH Guidelines*. Under Version B, Dr. Richard Haubrich's human gene transfer experiment (Protocol #9312-062) would have been exempt from RAC review. Dr. Haubrich's study involved the intramuscular injection of the retrovirus vector, HIV-IT(V), which encodes HIV-1 IIIB *env*. Version B would require long-term expression vaccines, e.g., certain influenza vaccines to be submitted for full RAC review.
Dr. Straus compared the differences between Versions A and B of Footnote 21: (1) Version B includes the term "human studies," which narrows the definition. (2) Version B includes the term "microbial immunogen," which limits the exemption to microbial immunogens and excludes other gene products. (3) Version A deletes the term "therapeutic," since the majority of vaccines are intended for prophylactic rather than therapeutic purposes. (4) Version B includes the term "persistence." Dr. Straus expressed his concern that the RAC should not exempt experiments in which the vector would persist or encode immunogens other than those of microbial origin. Dr. Post asked if the term "microbial" would encompass viruses. Dr. Straus responded that viruses would be considered "microbial."

Dr. Straus disagreed with Dr. Parkman's interpretation of the term "persistence." "Persistence" would be defined as biochemical persistence of the vector, not the immune response. Herpesviruses and adenoviruses are capable of long-term persistence in the body; therefore, not all constructs involving these viruses should be considered exempt. Dr. Walters asked whether Version B expands the scope of RAC review, e.g., including adenovirus vaccines, that have not been reviewed by the RAC previously. Dr. Straus acknowledged that Version B would exclude adenovirus vaccines; therefore, RAC review would be required. Ms. Grossman expressed her concern about adenovirus vectors. The wild-type virus persists in lymphocytes and different mutations of the virus introduced during construction of adenovirus vectors affect its persistence and immunological activity in the human body. Dr. Parkman agreed that these are reasons that adenovirus vectors should be reviewed by the RAC. Dr. Straus emphasized that advances in technology pose new safety issues, and that he would favor that these issues be resolved by the RAC in the public forum before exempting these vaccine constructs. Dr. Post said that vaccines exempted from the RAC review will still need to be approved by another government agency. Dr. Parkman explained that the majority of the recombinant viral vaccines that exhibit transient expression will be exempt from RAC review, e.g., poxvirus vectors. However, virus vectors that have the potential to persist in the body will not be exempt from RAC review, e.g., retroviruses, adenoviruses, herpesviruses, and papovaviruses. Vaccines involving persistent viruses may be encompassed by the *Accelerated Review* process that is

proposed as a separate agenda item for this meeting.

Committee Motion

A motion was made by Dr. Carmen and seconded by Ms. Grossman to approve Version B definition of Footnote 21 of the *NIH Guidelines* (exempt recombinant DNA vaccines). The motion to accept Version B passed by a vote of 13 in favor, 0 opposed, and no abstentions.

Footnote 21 will be amended to read:

"Human studies in which the induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encodedimmunogen is not expected, are not covered under Section III-A-4 of the *NIH Guidelines*. Such studies may be initiated without RAC review if approved by another Federal regulatory agency."

X. REPORT FROM THE RAC WORKING GROUP ON ACCELERATED REVIEW--AMENDMENT TO THE *NIH GUIDELINES* AND THE *POINTS TO CONSIDER* REGARDING ACCELERATED REVIEW OF HUMAN GENE TRANSFER PROTOCOLS/DR. PARKMAN

Minor Actions--Dr. Parkman

Dr. Walters called on Dr. Parkman, Chair of the RAC Working Group on *Accelerated Review*, to summarize the proposed amendments to the *NIH Guidelines* and *Points to Consider*. Dr. Parkman presented a flow diagram that outlined the proposed NIH review process for human gene transfer experiments. The proposed amendments define three categories of review: (1) RAC *Major Actions*, (2) NIH/ORDA *Minor Actions*, and (3) *NIH Director Actions*. Human gene transfer experiments considered as *Major Actions* are described under proposed Section IV-C-1-b-(1) of the *NIH Guidelines*. *Major Actions* require *Federal Register* announcement 15 days prior to the RAC meeting at which the proposal will be reviewed and an opportunity for public comment, full RAC review, and NIH Director approval. Human gene transfer experiments considered as *Minor Actions* are described under proposed Section IV-C-1-b-(2) of the *NIH Guidelines*. NIH/ORDA will determine whether a protocol qualifies as a *Minor Action* in consultation with the RAC Chair and one or more RAC members as necessary. A human gene transfer experiment that qualifies as an *NIH Director Action* is considered under proposed Appendix M-VI, *Single Patient Expedited Review Protocols*. A protocol considered as a *Single Patient Expedited Review Protocol* must be reviewed by extramural experts (may include intramural experts) and approved by the NIH Director. Protocols approved under the *Minor Action* and *Single Patient Expedited Review* categories will be reported by the RAC Chair at the next scheduled RAC meeting. Principal investigators of protocols approved under all review categories will be required to comply with the semi-annual data and adverse effect reporting requirements.

Dr. Parkman said that an additional category has been created for potential future use. These will be experiments that can be initiated simply by registration with NIH/ORDA, and the progress of the study will be tracked by the RAC.

Dr. Straus asked what kinds of experiments will be encompassed under the *Minor Actions* category. Dr. Parkman said that several categories of experiments will be discussed later, such as those involving lethally irradiated tumor cells. Another possible example will be a protocol moving from Phase I to Phase II and III trials. Some protocols will be moved from *Major* to *Minor Actions*; and in the future, possibly to the registration category. Dr. Straus suggested a minor change to the flow chart describing the review process

regarding reporting these actions to the next RAC meeting by the Chair. Dr. Parkman said that the NIH Director will have to make the decision to delegate authority to the RAC to approve *Minor Actions*. Dr. Wivel stated that a *Minor Action* is different from the single patient *Expedited Review* category, which requires approval from the NIH Director. All human experiments involving recombinant DNA will be tracked by the RAC except those vaccine studies that are considered exempt under Footnote 21 of the *NIH Guidelines*. Dr. Smith asked whether the *Minor Actions* will require IBC and IRB approvals prior to submission to ORDA. Dr. Parkman said that prior local approvals will be a condition for submission to ORDA.

Committee Motion--Minor Action

The RAC approved a motion made by Dr. Carmen and seconded by Dr. Straus to accept the amendments to the *NIH Guidelines* and the *Points to Consider* by a vote of 13 in favor, 0 opposed, and no abstentions. The proposed amendments will: (1) establish an *Accelerated Review* process (*Minor Actions*) for certain categories of human gene transfer experiments, (2) allow NIH/ORDA to assign the appropriate review category to all human gene transfer proposals that are submitted in compliance with the *NIH Guidelines*, and (3) allow NIH/ORDA to approve those categories of human gene transfer experiments that qualify as *Minor Actions* in consultation with the RAC Chair and one or more RAC members, as necessary. At their discretion, the RAC Chair and/or NIH/ORDA may determine that any proposal shall require review by the full RAC (*Major Action*).

Proposed Categories (Minor Actions)--Dr. Parkman

Dr. Parkman presented a draft document entitled: *Proposed Categories for Minor Actions to the NIH Guidelines Involving Human Subjects*. The proposed categories are considered guidelines for consideration and are not intended as a set of fixed categories. The proposed categories of *Minor Actions* are: (1) vaccines that are not considered exempt under Footnote 21, (2) lethally irradiated tumor cells/no replication-competent virus, (3) additional sites, (4) new Principal Investigator/new site, (5) "umbrella" protocols, (6) modifications not related to gene transfer, and (7) gene marking protocols.
The risk/benefit ratio will be applied to each individual protocol. Dr. Parkman described a hypothetical protocol in which irradiated retinoblastoma cells genetically modified to produce IL-2 will be administered to a child's eye. Although this experiment would be encompassed by the lethally irradiated tumor cell category, the serious clinical setting represents an increased risk/benefit ratio that would require an increased level of review, i.e., *Major Action*. However, the majority of experiments proposed under this category would qualify as *Minor Actions*. Dr. Wivel cited an example of injecting a plasmid DNA vector to a subcutaneous tumor mass vs. administering the vector DNA through a catheter to a lung metastasis. Dr. Parkman said that a protocol such as subcutaneous administration of irradiated cells producing IL-2 to a new tumor type such as prostate cancer would qualify for *Accelerated Review*.

Dr. Secundy and Ms. Grossman suggested that the working group define the criteria for *Minor Actions* to avoid arbitrary decisions. Dr. Parkman explained that establishing very rigid criteria would exclude a large number of proposals.

The RAC discussed the types of experiments that would be considered under the lethally irradiated tumor cell category. Dr. Parkman said that there are several possible options under this category: (1) a RAC-approved vector with an approved gene insert, (2) a RAC-approved vector with a new gene insert, (3) a modified RAC-approved vector, (4) a new tumor type, and (5) a new route of irradiated tumor cell administration. There should be no replication competent virus.

The RAC considered previously approved proposals initiated at new sites and/or by new Principal

Investigators. Dr. Straus and Ms. Grossman expressed their concern that new investigators may not possess adequate qualifications to conduct a duplicate study, and that such a situation may pose increased risk to the patients or the environment. Dr. Motulsky agreed that adequate qualifications is a major issue. Drs. Post, Parkman, and DeLeon assured the RAC that any proposal that presents such concerns can be elevated to the next full level of review, i.e., *Major Actions*.

Dr. Wivel raised a question regarding quality control in umbrella protocols. Would a single Principal Investigator be responsible for all study sites or a different Principal Investigator for each site? Dr. Parkman explained that the RAC-approved *Herpes simplex* virus thymidine kinase/Ganciclovir protocols to treat brain tumors are an example of studies that may qualify for *Accelerated Review*. The vector producing cells are prepared at a central facility and distributed to each site for administration to the patients by neurosurgeons; recombinant DNA expertise is not required in such a situation. Dr. Straus said that local expertise may be required at each site to perform assays such as examining the persistence of vector sequences in patients and assuring that these biological agents are not inadvertently released to the environment. Ms. Grossman agreed that issue is important. Dr. DeLeon said that competence of the Principal Investigator at each site will be a question for review. Dr. Post said that these are issues to be considered when the protocol is submitted for *Accelerated Review* and the RAC does not have to decide at this time.

With regard to protocols involving lethally irradiated tumor cells, Dr. Post said that such studies should be limited to RAC-approved vectors. Dr. Merchant asked whether direct *in vivo* administration of a vector to the tumor site would be considered a *Minor Action*. Dr. Parkman said that if the proposal represents any substantial change over a previously approved study, the experiment would be reviewed as a *Major Action*. Dr. Carmen asked whether the RAC-approved vector/new gene insert category includes any cDNA insert. Dr. Carmen expressed his concern regarding blanket inclusion of any cDNA insert even if the tumor cells are lethally irradiated. Dr. Parkman said that ORDA should review each proposal independently since certain cDNA inserts may pose risk, e.g., insertion of cDNA encoding for a toxin gene. Drs. Post, Straus, Secundy, and Ms. Grossman deliberated whether these exceptions should be specified or determined on a case-by-case basis when protocols are submitted for review. Dr. Parkman said that it is impossible to list all acceptable cDNA inserts for this category; therefore, the definition should be limited to RAC-approved vector constructs and RAC-approved vector constructs with minor modifications. Dr. Carmen expressed his support for this definition. Dr. Parkman suggested that RAC-approved protocols involving modification of the tumor type should qualify as a *Minor Action*; however, the issue of risk is always a consideration. Dr. Wivel assured the RAC that risk would be considered on a case-by-case basis at the time of submission.

Committee Motion 1 - Proposed Categories

A motion was made by Dr. Carmen and seconded by Dr. Dronamraju to modify the lethally irradiated tumor cell category as follows: lethally irradiated tumor cells/no replication-competent virus, RAC-approved vector constructs with minor modifications/additional tumor cells. The motion to accept this modification passed by a vote of 13 in favor, 0 opposed, and no abstentions.

Committee Motion 2 - Proposed Categories

A motion was made by Dr. Post and seconded by Dr. Straus to approve the following categories of *Minor Actions*: (1) non-exempt vaccines, (2) new site/original Principal Investigator, (3) new site/new Principal Investigator, (4) "umbrella" protocols, and (5) modifications not related to gene transfer. The motion passed by a vote of 13 in favor, 0 opposed, and no abstentions.

Dr. Merchant asked the RAC to consider Phase II and Phase III trials for consideration as *Minor Actions*. Dr. Straus stated that the RAC has considered very few Phase II gene transfer studies; therefore, it is premature to include such experiments as *Minor Actions*. Ms. Grossman and Dr. Parkman agreed with Dr. Straus' statement.

Committee Motion 3 - Proposed Categories

A motion was made by Dr. Smith and seconded by Dr. Post to amend the proposed categories of *Minor Actions* to include gene marking protocols involving RAC-approved vector constructs or RAC-approved vector constructs with minor modifications and/or additional target cells. The motion passed by a vote of 13 in favor, 0 opposed, and no abstentions.

Summary

The *Proposed Categories for Minor Actions to the NIH Guidelines Involving Human Subjects*, as approved by the RAC, reads as follows: (1) Vaccines -- Recombinant DNA vaccines not covered by Footnote 21, (2) Lethally irradiated tumor cells/no replication-competent virus -- RAC-approved vector constructs with minor modifications/additional tumor cells, (3) New site/original Principal Investigator -- RAC-approved protocol initiated at a new site (the original Principal Investigator is the same for the new site), (4) New site/new Principal Investigator -- RAC-approved protocol initiated at a new site (the Principal Investigator for the new site is different than the Principal Investigator of approved for the origina site), (5) "Umbrella" protocols -- RAC-approved protocol initiated at more than one additional site (Principal Investigator may be the same or different than the Principal Investigator approved for the original site), (6) Modification not related to gene transfer -- a modification to the clinical protocol that is no related to the gene transfer portion of the study, and (7) Gene marking protocols -- RAC-approved vector constructs or RAC-approved vector constructs with minor modifications/additional target cells.

XI. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* REGARDING *DELIBERATE TRANSFER OF A CHLORAMPHENICOL RESISTANCE GENE TO AN AVIRULENT STRAIN OF RICKETTSIA PROWAZEKI*/DR. POLICASTRO

Review--Dr. Post

Dr. Walters called on Dr. Post to present his primary review of the proposal submitted by Dr. Paul F. Policastro of the NIH, Rocky Mountain Laboratories, Hamilton, Montana. This request was deferred by the RAC at its June 7-8, 1993, meeting until the investigator returned to the full RAC with data demonstrating that the construct is safe and useful, and that there is a selective advantage of using chloramphenicol resistance over other selectable markers. Dr. Post explained that the investigator is requesting permission to introduce the chloramphenicol resistance gene into *Rickettsia prowazeki*. Chloramphenicol is one of the two antibiotics of choice to treat the human infection. This antibiotic resistant gene will be used as a selectable marker to establish a transformation system in eukaryotic host cells. Such studies will be valuable for conducting research on this fatally pathogenic organism. The investigator has responded to the RAC's initial concerns as follows: (1) the study will be confined to *Rickettsia prowazeki* Strain E, (2) a cloning vector is proposed that includes several safety features, and (3) the experiment will be conducted in a BL3 facility. The chloramphenicol resistant strain will be used only to develop the transformation conditions; other selectable markers will be developed to perform subsequent research. Although the proposal is reasonable with regard to the molecular biology aspects, Dr. Post deferred to the opinion of infectious disease experts with regard to safety issues.

Review--Dr. Straus

Dr. Straus explained that Strain E *Rickettsia* is of reduced virulence but is not avirulent. Although Strain E has been used as a human vaccine, the strain is probably capable of reversion to a virulent form after "n" number of *ex vivo* passages. In Dr. Policastro's submission, he states that Strain E has been reported to revert to virulent phenotypes after 13 serial passages in the lungs of albino mice and upon brief passage in pigs under heavy inoculation. Symptoms of human infection with Strain E have been observed following exposure to high titers, i.e., between 1 x 106 and 1 x 107 infectious organisms. The proposed experiment will require manipulating the organism at the levels of 1 x 1011 infectious organisms or more. The introduction of the chloramphenicol resistance gene will eliminate one of the two antibiotics (chloramphenicol and tetracycline) known to be effective in the treatment of a human infection, louse-borne typhus. Dr. Straus stated that if there are known deletions of the virulence genes, the organism cannot revert to a virulent form, or the organism is crippled in some other way, he would recommend approval of this request; however, considering the significant safety concerns, the RAC should not set a precedent by approving this proposal even for a one-time experiment under BL3 containment.

Other Comments

Dr. Parkman suggested an alternative to disapproving this request. The RAC could recommend approval with the stipulation that any residual bacterial stocks be destroyed once the transformation experiment has been conducted.

Dr. Straus said that there is no absolute scientific reason for inserting the chloramphenicol resistance gene. Although the investigator has stated that chloramphenicol resistance is the selectable marker of choice, other options are available. Dr. Straus said that he would recommend approval of this experiment only in a Biosafety Level 4 containment facility and contingent on the destruction of any residual bacterial stocks once the experiment is performed. The RAC should not set a precedent for this type of experiment.

Dr. Motulsky inquired about the scientific merit of this experiment. Dr. Straus explained that the biology of *Rickettsia* organisms is not well understood. These bacterial pathogens cause serious human disease, e.g., Rocky Mountain Spotted Fever and typhus-like syndromes. This organism has been known to cause devastating illness (typhus) in wartime. Currently, there is no vaccine for typhus. Dr. Straus stated that the objective of such research is extremely valuable; however, a selectable marker other than chloramphenicol resistance would be preferable.

Dr. Post said that in consideration of the serious safety concerns raised by Dr. Straus, this request should be deferred until the investigator proposes an alternative request, e.g., use of a Biosafety Level 4 facility, alternative selectable marker, etc.

Dr. DeLeon asked whether the investigator submitted additional data since the previous review. Dr. Post answered that additional data was not provided, only a more detailed description of the proposed experiment.

Dr. Walters asked whether there is any genetically modified *Rickettsia* that would be less virulent. Dr. Straus said that for many bacteria the virulence genes are not well-defined. He cited a recently published document showing that it is possible to create an experimental environment in which the organism has reduced virulence. Under this condition, experiments using virulent organisms can be performed. It might be worthwhile to attempt to produce avirulence in culture and then transfer the organism to animals where there is the possibility of upregulating certain genes that will restore virulence.

Dr. Straus said that the investigator has stated that at low multiplicity of infection, this organism (Strain E)

causes only mild disease in humans, a condition used for vaccine studies. But in the proposed experiments, the laboratory personnel are expected to be exposed to higher doses of the organism that could cause serious symptoms. Dr. Carmen asked about possible Biosafety Level 4 facilities. Dr. Wivel stated that there are four such facilities in the United States.

Committee Motion

A motion was made by Dr. Post and seconded by Dr. DeLeon to defer the proposal. The proposal was deferred by a vote of 13 in favor, 0 opposed, and no abstentions. The proposal was deferred based on the following: (1) chloramphenicol is one of the two antibiotics of choice for the treatment of *Rickettsia* infection; (2) strain E (proposed for this study) is considered to be of reduced virulence not avirulent; Strain E has been reported to revert to the virulent state after passages *ex vivo*; and (3) data is unavailable demonstrating the probability of reversion to a virulent strain when grown under large-scale conditions, i.e., between 1 x 109 and 1 x 1010 organisms.

The RAC discussed possible scenarios under which this proposal might be eligible for resubmission for RAC review: (1) if the gene encoding for virulence were identified, or (2) the investigator submits a request for use of this organism in a Biosafety Level 4 facility contingent on the destruction of residual stocks upon optimization of transformations assays. The RAC emphasized that resubmission of the proposal will not guarantee RAC approval.

XII. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: *PHASE I STUDY OF IMMUNOTHERAPY FOR METASTATIC RENAL CELL CARCINOMA BY DIRECT GENE TRANSFER INTO METASTATIC LESIONS*/DR. VOGELZANG

Review--Dr. Do

Dr. Walters called on Dr. Doi to present his primary review of the protocol submitted by Dr. Nicholas J Vogelzang of the University of Chicago, Chicago, Illinois. Dr. Doi explained that the proposed study very similar to Dr. Gary J. Nabel's (Protocol #9306-045) and Dr. Joseph Rubin's (Protocol #9312-064 previously approved by the RAC. This study will be conducted on 15 HLA-B7 negative patients with metastatic renal cell carcinoma. Patients will receive direct intratumoral injections of a cationic lipos complex containing the plasmid vector, pHLA-B7/-2 microglobulin . This vector expresses a heterodim cell surface protein consisting of HLA-B7 and -2 microglobulin . Expression of this protein should induc an *in vivo* antitumor immune response. The objectives of this study are to determine a safe and effecti dose of the vector, confirm *in vivo* expression, and characterize the immune response. The only difference between this proposal and those of Drs. Nabel and Rubin is the tumor type (renal cell carcinoma

Dr. Doi asked the investigators to respond to the following questions: (1) Is novel information expecte based on the new tumor type? (2) Would there be an advantage in waiting for the results of Drs. Nabel and Rubin's studies? (3) How many Phase I studies of an identical protocol, but with different tumor types, are required to obtain significant information? He stated that this protocol is an ideal example of an experiment that would qualify for the *Accelerated Review* process, provided that the Informed Consent documents adopted by different institutions are properly reviewed.

Review--Dr. DeLeo

Dr. DeLeon agreed with Dr. Doi's statement regarding the eligibility of this protocol for *Accelerated Review* process. Dr. DeLeon inquired about the expertise of the investigators at the new site; particula the personnel involved in the needle biopsies of the tumor nodules. Dr. DeLeon stated that she wa

satisfied with responses and additional information provided by the investigators. Dr. DeLeon mad several specific suggestions for improving the Informed Consent document: patient follow-up should be life-long and the words, "treatment" and "therapy," should be replaced with "procedure." There are several inconsistencies between the protocol and the Informed Consent document describing the treatment procedures. Dr. DeLeon said that most of the suggestions provided in her written review were accepte by the investigators. Dr. DeLeon recommended approval of the protoco

Other Comments

Dr. Carmen said that preclinical animal experiments using renal cell carcinoma cells were not provided. Dr. DeLeon noted that extensive animal experiments were submitted to support Dr. Nabel's origi protocol. Dr. Parkman explained that based on published data (IL-2 and TIL administration), renal cel carcinoma is the second most responsive tumor type to immunotherapy. Since enhanced antitumor responses have been demonstrated in Dr. Nabel's melanoma protocol, renal cell carcinoma is logicall the next tumor to study. Dr. Post said that animal studies are not totally predictive for the human immune response; therefore, animal studies should not be an absolute prerequisite for these human trials.

Ms. Grossman inquired whether Dr. Nabel will have an interactive role with the Principal Investigators a the other sites. Where is the central laboratory located that will perform the immunological assays? How will the results obtained from this multi-center trial be collected and evaluated? How will quality control be assured? Dr. Walters inquired about the most frequent metastatic sites of renal cell carcinom

Investigator Responses--Dr. Vogelzan

In response to Dr. DeLeon's question about the qualifications of the investigators, Dr. Vogelzang st that Dr. Gary Sudakoff will perform the sonographically -guided needle biopsy. Dr. Sudakoff pos great deal of expertise in performing this technique and his biographical sketch has been submitted for review. Responding to Dr. Walters' question about frequent metastatic sites, Dr. Vogelzang said tha renal cell carcinoma metastasis are in visceral organs such as the lung, liver, mediastinal , an retroperitoneal lymph nodes. Such locations are in contrast to the subcutaneous sites of metastases in melanoma patients. In response to Ms. Grossman's question, Dr. Vogelzang stated that Dr. Nabel be directly involved in this study. The multi-center trial will be coordinated by Vical , Inc., San Diego California, and the company has selected a central laboratory to perform the immunological assays. Dr. Parkman asked about the size of the tumor in relation to the dose of DNA to be injected. Dr. Vogelzang said that most metastatic tumors are 2 to 4 cm in diameter. The primary tumors are much larger an necrotic and are not suitable for injection.

Dr. George Gray explained that Dr. Nabel has served on the Scientific Advisory Board of Vical , Inc. has chaired the Oncology Task Force that decides issues such as the tumor types and institutions that wil be involved. Dr. Evan Hersh , Principal Investigator of the Arizona Cancer Center study, will oversee th central laboratory that will perform the immunological assays for all sites. Vical will establish th procedures for testing and evaluate the results from all study sites. Dr. Nabel is conducting a independent protocol that is not considered part of this multi-center study. Dr. Nabel has an investigato sponsored IND , whereas, Vical has an institutional sponsored IND. Dr. Doi asked about the pro DNA/liposome dose as compared with that of Dr. Nabel's study. Dr. Gray responded that the present d of 10, 30, and 300 micrograms is bracketed between the highest and the lowest dose of Dr. Nabel's st i.e., 3 to 500 micrograms.

Dr. Walters stated that the abstracts contain language that implies that there is a therapeutic intent. Such language is not appropriate for a Phase I study. Dr. Vogelzang responded that the abstracts will b

modified to reflect this concern.

Committee Motion

A motion was made by Dr. DeLeon and seconded by Dr. Doi to approve the protocol. The motion p by a vote of 13 in favor, 0 opposed, and no abstentions.

XIII. ADDITION TO APPENDIX D OF THE *NIH GUIDELIN* REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: *PHASE I STUDY OF IMMUNOTHERAPY OF MALIGNANT MELANOMA BY DIRECT GENE TRANSFER* **/DRS. HERSH, AKPORIAYE, HARRIS, STOP UNGER, AND WARNEK**

Review--Dr. Do

Dr. Walters called on Dr. Doi to present his primary review of the protocol submitted by Dr. Evan M. H of the Arizona Cancer Center and Drs. Emmanuel Akporiaye, David Harris, Alison T. Stopeck, Evar Unger, and James A. Warneke of the University of Arizona, Tucson, Arizona. Dr. Doi said that t protocol is similar to other protocols previously approved by the RAC, i.e., Dr. Gary J. Nabel's (Protoco #9306-045), and Dr. Joseph Rubin's (Protocol #9312-064), and Dr. Vogelzang's protocol that was jus reviewed and recommended for approval by the RAC. Like Dr. Nabel's protocol, this study involve melanoma patients. However, larger doses of the DNA/liposome complex are proposed for this study. These doses are in the same range as Dr. Rubin's colorectal cancer protocol. This Phase I protocol is a part of the multicenter study sponsored by Vical, Inc., to evaluate the safety and immune responses direct intratumoral injection of DNA/lipid complexes containing the nonviral plasmid DNA vect pHLA-B7/-2 microglobulin. This vector expresses a heterodimeric cell surface histocompatibility ant which should elicit an *in vivo* antitumor response. Dr. Doi stated that the same comments regarding Vogelzang's protocol also apply to Dr. Hersh's proto

Review--Dr. DeLeo

Dr. DeLeon stated that the term "at two additional sites" should be deleted from the *Points to Consider* since only a single site is proposed for this study, the Arizona Cancer Center. There are several inconsistencies between the protocol and the Informed Consent document with regard to the study design. The protocol states that patients in study Arm 1 will receive a single injection, whereas the Informed Consent document states that multiple injections will be administered to a single nodule (up to 5 times). In the investigators' written response they explained that up to 5 points of injections will be administered into the same tumor mass to maximize contact between the DNA liposome and tumor cells.

Other Comments

Ms. Grossman said that a request for autopsy was inadvertently omitted from the Informed Consent document, and that the number of patients proposed for this study was not clearly stated in the protocol.

Dr. Walters noted a statement in the Informed Consent document regarding compensation for research related injuries. The original document stated, "in the unlikely event of physical injury resulting from research procedures, the University will provide first-aid medical treatment. Treatment from injuries or side effects directly related to this experimental treatment will be provided at no cost to you." However, the revised document states "Necessary emergency medical care directly related to this treatment will be provided from Evan M. Hersh, M.D." Ms. Grossman inquired about the exact number of patients who w

be entered onto the study. Dr. Walters inquired about the reason for this change. Dr. Secundy aske whether a request for autopsy has been included in the revised Informed Consent document.

Investigator Response--Dr. Hers

Dr. Hersh said that Dr. DeLeon's suggestions regarding "single site" language and a request for au will be incorporated into a revised Informed Consent document. Responding to Dr. Walters' question about compensation for research injuries, Dr. Hersh said that the revised language was suggested by IRB of the Arizona Cancer Center. Any medical costs associated with toxic side effects of investigation drugs will be covered by the insurers or third party payers. Regarding the number of patients in the trial, Dr. Hersh said that 15 " evaluable " patients will be entered onto the st

Dr. Steven Kradjian of Vical responded to Dr. DeLeon's question about the number of study site agreed to submit a revised *Points to Consider* document that specifies a single site, the Arizona Cancer Center. Dr. Hersh said that a request for autopsy will be added to the Informed Consent document an submitted for IRB approva

Committee Motion

A motion was made by Dr. Doi and seconded by Dr. DeLeon to approve the protocol contingent on and approval of the following: (1) a revised statement in the Informed Consent document indicating that ar autopsy will be requested in the event of death (including IRB approval), and (2) a revise *Points to Consider* document that specifically addresses a single site, the Arizona Cancer Center. The motion to approve the protocol passed by a vote of 13 in favor, 0 opposed, and no abstentions.

There was a follow-up discussion on the issue of autopsy request. Dr. Vogelzang said that the stateme was omitted from the Informed Consent document because he considered it improper to require patient autopsy for participation in the trial. Dr. Parkman explained that the RAC does not require an autopsy; however, it is recommended that a statement requesting autopsy should be included in the Informed Consent. Dr. Hersh agreed to coordinate with Dr. Vogelzang to have this statement included in revised Informed Consent document.

XIV. REPORT ON THE GENE THERAPY ADVISORY COMMITTEE (GTAC) OF THE UNITE KINGDOM/MR. TAYLOR

Mr. Anthony Taylor, Secretariat of GTAC , United Kingdom, provided the RAC with an overview of th activities of this committee which is responsible for review of human gene transfer proposals in the United Kingdom. Mr. Taylor explained the origin of GTAC . GTAC was established following the recommen of the Clothier Committee in 1991 that endorsed the concept that gene therapy should be considered as a mainstream approach to medical research and should be subjected to all the ethical considerations of medical research. This concept was endorsed at the parliamentary level in the United Kingdom and GTAC was established within the Department of Health to provide oversight of gene therapy researc within the United Kingdom. GTAC will report on developments in gene therapy to the Secretary of Stat for Health. GTAC is chaired by Dr. Judith Lloyd, former Professor of Pediatric Medicine at the Universit London. GTAC is composed of 16 members: 8 of whom possess expertise in the areas of medicine an science, and 8 who represent expertise in such areas as clinical psychology, genetic counseling, industry, law, ethics, nursing, and the media. He noted that one member is a leading British Broadcasting Company journalist.

GTAC has approved 6 human gene transfer trials to date; two of these trials are currently in progress, for the treatment of cystic fibrosis and one for the treatment of adenosine deaminase deficienc

(Netherlands collaboration). Studies that have not yet been initiated involve: (1) cytokine-mediated therapy in malignant melanoma, (2) a neuroblastoma marking study (United States collaboration), and a lymphoma vaccine trial. These trials are currently awaiting approval from the Medicines Control Agency (the United Kingdom's equivalent of the Food and Drug Administration). GTAC is currently in the progr of reviewing an additional 4 studies involving cancer, cystic fibrosis, and HIV infection.

GTAC differs from the RAC in that its meetings are not open to the public. However, Principa Investigators are encouraged to publish their protocols in appropriate journals, and GTAC is considerir the publication of an annual technical report regarding the activities of the committee. GTAC does no operate under statutory regulations; however, the Department of Health guidelines require that GTAC review all human gene transfer proposals. All biomedical research in the United Kingdom must be reviewed and approved by local research ethics committees.

Dr. Parkman asked how often the GTAC meets and how its review process differs from the RAC revie Mr. Taylor responded that the Secretariat and the Chairman of GTAC screen all human gene transfe studies prior to GTAC review. The committee review is very similar to the RAC review in that one or tw primary reviewers are assigned for each proposal. GTAC currently meets 5 times a year; however, thi schedule may be modified to accommodate 6 meetings a year. Essentially, a given proposal will be cleared within a 3-month period. Dr. Motulsky inquired whether the gene transfer studies proposed in t United Kingdom differ from those approved by the RAC. Mr. Taylor responded that 3 of the first 6 trials approved by the GTAC utilized non-viable DNA/liposome or plasmid DNA delivery systems. Ms Grossman asked whether there is any data reporting system to monitor research progress. Mr. Taylor saic that the gene therapy trials are still in the very early stage in the United Kingdom and no such system has been in operation yet. Dr. Post asked whether there is any plan to establish a registry to track patients who have received gene therapy. Mr. Taylor responded that the plan to establish a registry is under consideration. Dr. Doi asked about coverage of the medical costs in the United Kingdom regarding ger transfer studies. Mr. Taylor explained that the National Health Service covers all medical costs. Dr. Smith asked whether there is any reimbursement to the National Health Service for trials sponsored by a company. Mr. Taylor responded that there is no system to recoup the costs for company-sponsored research. All the current studies are funded by the government and non-profit charities. Dr. Motulsky asked if Mr. Taylor knew of any additional oversight committees for human gene therapy besides the United States and the United Kingdom, such as other European countries or Japan. Mr. Taylor responded that Japan has recently established a dual mechanism for reviewing gene therapy protocols. In the Netherlands, Denmark, and Germany, protocols are reviewed through existing national advisory committees on genetic modifications.

Dr. Marcel made an unofficial report on gene therapy review in France. There is a committee under both the Ministry of Research and Ministry of Agriculture that oversees viral biosafety and scientific issues c human gene therapy. Six proposals have been reviewed including studies of gene marking and gene transfer in diseases such as adenosine deaminase deficiency, cystic fibrosis, glioblastoma , melanoma. In France, once a proposal is approved by this dual committee, the clinical trial can be initiated without further review by other agencies.

Dr. Walters remarked that recently a report has been published entitled: *Experimental (Somatic) Gene Therapy, Ethical Concerns and Controls* from Dr. M.A.M . de Wachter , Instituut voor Gezon Maastrict , The Netherlands. This report surveyed human gene transfer studies and their oversigh mechanisms in Europe. Once permission has been obtained from the publisher, copies will be made available to RAC members.

<u>XV</u>. ADDITION TO APPENDIX D OF THE *NIH GUIDELIN* REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: *CLINICAL PROTOCOL FOR MODIFICATION OF ONCOGENE*

Review--Dr. Motulsk

Dr. Walters called on Dr. Motulsky to present his primary review of the protocol submitted by Dr. Jack / Roth of the MD Anderson Cancer Center, Houston, Texas. This protocol is a resubmission of a protocol that was contingently approved by the RAC at its September 1992 meeting. At its December 1993 meeting, the consensus of the RAC was that Dr. Roth should resubmit a revised protocol (including all additional data for review by the full RAC) based on the following: (1) failure of the primary reviewers to recommend approval of the protocol, (2) lengthy delays that occurred, (3) there are several new members on the RAC who were not on the committee at the time the original protocol was reviewed, and (4) Dr. Roth requested the use of a substitute vector. The RAC agreed that new primary reviewers would be assigned for the resubmitted protocol. The RAC informed Dr. Roth that this study was considered administratively inactivated; therefore, RAC approval of the protocol was withdrawn.

Dr. Motulsky explained that recent scientific advances have led to an understanding of oncogenes (K- *ra*and their role in tumor cell proliferation) and tumor suppressor genes (i.e.,*p53* and their role in suppressing tumor growth). Although normal *p53* is a tumor suppressor gene, introduction of certain mutations can confer oncogenic capacity*p53*. The investigator proposes to use the retroviral construct, AS-K- *ra*, to express antisense RNA in an attempt to block the function of the *ra* oncogene . Anothe construct, LN*p53*B, will be employed to express wild-type *p53* in an attempt to suppress tumor growth. Most of the preclinical animal experiments were performed with the retroviral construct LNSX-*p53*, which is different from the vector currently proposed for the human study. Additional studies have been submitted in a human lung tumor/nude mouse model demonstrating marked suppression in tumor growth in response to intrabronchial injection of the LNp53 construct. The RAC must consider the likelihood th suppression of tumor growth in a murine model will correlate with the human respons

Dr. Motulsky stated that the RAC was previously concerned whether the constructs demonstrate biological activity and whether rearrangements in the vector structure are likely to occur during vector propagation. The Southern blot data submitted is uninterpretable . The principal investigator ha adequately responded to previous concerns about the sensitivity of the assays for detecting the transforming potential of the proposed constructs. The data demonstrates that the assay system will provide adequate sensitivity.

Dr. Motulsky recommended approval of this study based on biologic plausibility; however, othe reviewers' concerns about vector rearrangements, etc., must be addressed before full RAC approval can be recommended.

Review--Dr. Haselkorn (presented by Dr. Motuls

Dr. Motulsky summarized the written review submitted by Dr. Haselkorn . Non-small cell lung carcin has a very poor prognosis. Molecular analysis has revealed that mutations in the*p53* tumor suppressor gene and in the K- *ra* oncogene account for the majority of cases of this type of cancer. Therefore, the targeted to these genes seems justified. Patients will be eligible who have inoperable lung cancers, who are not responsive to radiation, and who demonstrate a high probability of dying from pneumonia caused by blockage of the lung by the tumor mass. Following surgical debulking of the tumor mass b bronchoscopy , the residual tumor will be injected with retroviral constructs that express either th wild-type *p53* gene or an antisense RNA to prevent translation of the mutated *ra* oncogene . Th previous review raised three major issues: (1) the ability to detect transforming viruses, (2) demonstration of adequate biological activity, and (3) demonstration of the "bystander" effect in*in vitro* cell mixing

experiments. The "bystander" effect on tumor growth was observed in animal experiments. The first two concerns have been satisfactorily addressed by the investigator. The mechanism of the "bystander" effect remains unknown; however, absence of knowledge about the mechanism should not prevent the protocol from being approved. The investigators should explain why the *p53* gene does not induce apoptosis in all cell lines.

Review--Ms. Grossman

Ms. Grossman raised several serious concerns regarding the vectors used in this protocol. How will quality assurance of the clinical grade retroviral constructs to be administered to patients be maintained? The Southern blot analysis of vector DNA, which demonstrates the absence of vector rearrangement, is uninterpretable . The size of the DNA bands are inconsistent with the *p53*B construct. She asked the investigator to respond to Dr. Miller's written comments that the LN*p53*B construct has the propensity to undergo rearrangement in vector structure during viral propagation due to the bidirectional SV40 polyadenylation signa

Ms. Grossman stated that the "bystander" effect attributed to the present system is different from the "bystander" effect observed in the herpes simplex virus thymidine kinase / ganciclovir protocols biological mechanism of the latter phenomenon is more clearly understood.

Ms. Grossman said that although Dr. Roth is a reputable physician qualified to conduct a study on small-cell lung cancer, there are serious concerns about the molecular biology aspects of this proposal.

Other Comments

Dr. Post asked whether the sensitivity of the assay for transforming viruses is adequate since this issue was a major concern during the previous review. Ms. Grossman asked what construct was assayed for transforming virus. Dr. Motulsky asked the investigators to clarify exactly what constructs are proposed the human study. In addition, Dr. Post noted that large volumes of vector supernatants will be administered to these patients. Will there be any effect of these oncogene and antioncogene vector normal cells?

Dr. Parkman inquired about what is the rate of transduction in the animal tumor model. How does the rate of transduction relate to the efficacy of suppressing tumor growth in animals? Are these data reproducible? Dr. Parkman asked Dr. Roth to address the issue of vector structure in the clinical grade supernatants.

Investigator Response--Dr. Roth

Responding to Dr. Post's question on the effect of normal human cells upon transduction, Dr. Roth said that vectors expressing either the antisense *ra* or the wild-type *p53* gene demonstrate no appreciable *in vitro* effect on the proliferation of normal fibroblasts unless the *p53* gene is expressed at an extremely high level.

Dr. Roth made a short presentation about his protocol with illustrations in an attempt to address several general questions. Dr. Roth said that the eligible patients must have bronchial obstruction that is untreatable with conventional therapy and have an expected survival of 4 to 6 months. The proposed treatment is intended to slow tumor growth rather than be curative. Following a biopsy, a determination will be made as to whether the tumor has K- *ra* or *p53* gene mutation. Based on this information, the appropriate construct will be administered. Following partial endoscopic resection, the tumor bed will b

irrigated with vector supernatants daily for 5 days through a bronchoscope. This treatment will be repeated monthly.

Dr. Parkman noted that there is reproducible therapeutic effect in the animal studies. A maximal response is obtained at a multiplicity of infection of 5 retroviral particles per tumor cell, but the response decreases to one-half when the ratio is decreased to one-third. Dr. Parkman asked about the multiplicity of infection that would be expected in the clinical protocol. In the animal experiments, all tumor cells are in cycling and are susceptible to viral integration in the 24 hour period of treatment. What percentage of cells in human tumors will be in cycling? Dr. Roth answered that cell cycling problems will be overcome by administering repeated injections. Since the bulk of the tumor will be removed by laser treatment, a multiplicity of infection of 5 viral particles to one tumor cell is achievable.

Responding to the question of the size of DNA fragments in the Southern blot analysis of cells transduce with the LN*p53*B vector, Dr. Roth said that digestion with the Kpn restriction enzyme should yield fragment approximately 8.7 kb. Ms. Grossman questioned the validity of the Southern blot data submitted by Dr. Roth. This data shows that DNA fragments of the same size of 10.8 kb are detected in cells either transduced by the LNSX vector or by *p53*B construct with gene insert. Dr. Roth said that he was not sure why the DNA fragment migrates aberrantly at this point. Dr. Straus said that the DNA fragment with the *p53* gene insert should not migrate at the same rate as the fragment obtained from the vector itself. Dr Roth said that the present 1% gel analysis will not permit resolution of this difference. Drs. Straus, Post, and Ms. Grossman said that the size difference should be approximately 5.5 kb, and it should be resolved in this gel analysis. Ms. Grossman asked whether Northern blot analysis of vector RNA in transduced cells has been performed in order to determine whether there is any vector structure rearrangement. Dr. Roth referred to a letter by Dr. Harry Findlay of Emory University, Atlanta, Georgia, which states that the transduced *p53* expression was detectable in his Northern blot analysis. Ms. Grossman said that the data is not presented to answer her question on vector rearrangement. Ms. Grossman remarked that from her understanding of the situation that every time the principal investigators at Genetic Therapy, Inc., Gaithersburg, Maryland, have made a production run on this virus, they found vector rearrangement. Dr. Roth said that they are using a different vector construct and a different producer cell line. Ms. Grossman said that vector rearrangement is an important issue to be resolved before proceeding to human trials. She said that the data presented is not convincing.

Responding to questions about the "bystander" effect, Dr. Roth presented data reported in his published paper entitled: *A Retroviral Wild-type p53 Expression Vector Penetrates Human Lung Cancer Spheroids and Inhibits Growth by Inducing Apoptosis*, published in *Cancer Research* (Vol. 53, pp. 4129-4133, 1993). This data demonstrated that substances released from *p53*-induced apoptosis inhibit tumor cell growth. Dr. Roth said that very recent data suggested that this substance may be a protein molecule since its activity is destroyed by protease digestion. This observation may offer a possible explanation for the mechanism of the "bystander" effect observed in the animal model.

Dr. Roth said that he is unable to perform the cell mixing experiment to demonstrate that cells transduce with *p53* are capable of inhibiting the growth of untransduced cells. Cells transduced with *p53* gene construct undergo apoptosis, and they cannot be established as a cell line.

Responding to Dr. Parkman's question on *in vivo* transduction efficiency, Dr. Roth presented data demonstrating approximately 60% transduction efficiency in an orthotopic human lung cancer nud mouse model. These data has been subjected to biomathematics analysis with confidence intervals between 30 to 100%. Dr. Roth said that this number is unexpectedly high. Dr. Straus questioned the interpretation of this data. Some of the effect could be explained by the DNA copy number per cell since Dr. Roth assumed that every DNA copy represents a cell. Dr. Roth said that single copy integration has

been observed in the cell line. Dr. Parkman said that 60% efficiency would not be surprising for the transduction of a cell line if 100% of cells are in cell cycling. What percentage of wild-type tumor cells are in cycling? Dr. Roth said that he does not know the answer to that question. Dr. Lang Chang, Institute of Biomedical Sciences, Academia Sinica, Taipei, from the audience questioned the interpretation of th data on transduction efficiency.

Dr. Roth said that the antitumor effect of the retroviral constructs on the tumor growth is reproducible a significant, regardless of the underlying mechanism. Ms. Grossman emphasized that precise knowledge about the proposed constructs is essential for human studies. The RAC should not recommend approval of a human trial if the vectors to be applied to humans are not adequately characterized. Again, Ms. Grossman raised questions on uncertainty regarding the size of DNA fragments from Kpn digests o vector transduced cells. Dr. Roth conceded that uncertainty resulted from the problem that the sequen of the vector is not presented, thus, he is unable to provide size information.

Dr. Straus said that the animal data is impressive and justifies the human study. However, Dr. Straus agreed with Ms. Grossman's comment that a complete sequence of the vector construct is essential, and data demonstrating the integrity of the vector structure is necessary in order to proceed with the human study. Dr. Post said that the mechanism of the "bystander" effect and transduction efficiency in the animal model are not major issues; however, the complete vector sequence and the Southern blot data on the vector structure are essential. Dr. Post expressed his dissatisfaction with the data regarding the size of the DNA fragments, the Southern blot, and generally the characterization of the vector structure.

Dr. Roth showed a DNA sequence of the vector in an attempt to address the question of the Kpn fragm size. Dr. Roth said that in this sequence, a large section of the actin promoter of the vector is not incluc Dr. Post said that this missing sequence information appears to be the source of some of the uncertainty regarding the DNA fragment size. Dr. Post said that this missing information raises another question of whether there is another Kpn site within this actin promoter segment. Kpn was originally presum principal investigator to be a single cut enzyme that digests the DNA at a single site in each of the two long terminal repeat regions of the vector. Dr. Roth said that an additional Kpn site is unlikely since onl two predicted DNA fragments are generated by digestion with Kpn . Ms. Grossman questioned the dat since the digests of the construct with the insert are the same as the vector by itself. Dr. Straus said that the gel experiment presented should be able to distinguish a size difference of 4 kb between the fragments from the vector and the construct with the insert according to the molecular size markers included in this experiment. Dr. Parkman said that the data presented is of such poor quality that it cannot be accepted as a basis for protocol approval. A large segment of vector sequence not accountable is not acceptable.

Ms. Grossman emphasized that for approval a vector must be completely sequenced or a detailed restriction enzyme map provided. A Southern blot analysis of cells transduced with the antisense *ra* and *p53* retroviral constructs, and a comparison with the LNSX vector control will be required. In additi the Northern blot data on vector transcript should be provided. Dr. Roth said that Northern blot analysis will be difficult for tumor RNA.

Dr. Motulsky stated that although the animal data is impressive, a full characterization of the vectors i essential for this protocol.

In terms of characterization of the vector structures regarding both retroviral constructs containing the antisense *ra* and *p53* genes, Drs. Post, Straus, and Ms. Grossman stated that the following informatior is necessary: (1) the complete DNA sequences of the vector constructs, (2) a detailed restriction enzyme digestion map of the constructs, and (3) a series of Southern blot analyses of vector DNA from cells

transduced with the parental vectors versus constructs containing the gene inserts. Data should b obtained from several transduced cell lines demonstrating concordance with the restriction enzym analysis and the restriction map.

Committee Motion

A motion was made by Dr. Straus and seconded by Dr. Parkman to approve the protocol. Approval of the protocol is contingent on the review and approval of the following data for both the K- *ra*and *p53* retroviral constructs by the primary reviewers and Drs. Post and Straus: (1) complete vector sequences, including detailed restriction enzyme maps relevant to the LNSX backbone and the gene inserts; and (Southern blot analyses using several transduced cell lines, including cell lines transduced with the constructs with and without gene inserts, demonstrating concordance with the restriction enzyme analysis and sequence data. The motion to approve the protocol passed by a vote of 13 in favor, 0 opposed, and no abstentions.

XVI. CHAIR REPORT - OUTGOING MEMBERS

Dr. Walters noted that several members of the RAC have completed their term of service. He thanked Drs Carmen, Hirano, Post, Geiduschek and Krogstad , and Ms. Grossman, for their dedication, expertis tireless efforts, which have contributed significantly to the advancement of human gene therapy.

XVII. REPORT FROM THE WORKING GROUP ON INFORMED CONSENT - AMENDMENTS TO PART I-D OF THE *POINTS TO CONSIDER*/DR. ZALLE

Dr. Gary Ellis, Director of the NIH Office for Protection from Research Risks, recommended severa avenues that should be pursued by the RAC with regard to the "quality and content of Informed Consent documents into constructive changes in the informed consent process," specifically in relation to human gene transfer, during his oral presentation to the RAC on December 4, 1993, and in his memorandum dated December 23, 1993. Dr. Ellis recommended that the *Points to Consider* should be amended to introduce consistency in the Informed Consent document language.

Dr. Zallen , Chair of the RAC Working Group on Informed Consent, said that in order to reduce th frequent problem of inadequately prepared Informed Consent documents and because of the importance of informed consent issues in clinical research, a working group has been formed to amend Part I-D, Informed Consent, of the *Points to Consider*. The working group includes: Ms. Buc , Mr. Capron, Ms Meyers, Drs. Krogstad , Motulsky , Secundy , and S

Dr. Zallen said that frequently investigators do not adequately address informed consent questions in t preparation of the *Points to Consider*. Dr. Zallen provided two versions of the revised Part I-D: (1) th version drafted by the working group, and (2) a modified version incorporating modifications suggested by Mr. Capron. The first version attempts to separate the informed consent process from the Informed Consent document. Ms. Meyers recommended inclusion of a statement indicating that subject selection should be equitable. The second version has been modified according to Mr. Capron's suggestions to consolidate the consent process and consent document in a single section in the Part I-D.

Dr. Zallen said that questions on how informed consent is obtained from study subjects is very importa considering the recent scandal involving radiation research performed during the 1940s and 1950s. She would prefer the first version to have the informed consent process separated from the document. The second version has incorporated a more simplified and polished language suggested by Mr. Capron.

Dr. Straus expressed his concern that it is difficult for principal investigators to describe very intimate personal interactions involved in the consent process. Dr. Parkman added that an effective informed consent process may vary depending on a particular disease to be treated and the ethnic background of a participating subject. Dr. Secundy stated that the informed consent process can be well written. There trained individuals with expertise in this area who can deal with this process effectively, and the qualification of these experts can be evaluated from their curriculum vitae. Dr. Parkman disagreed on the need for another trained expert to obtain informed consent. Dr. Straus inquired what will be the qualification of such individuals. Dr. Secundy said that those are persons trained in bioethics, social wo and communication skill. Demonstrating sensitivity to these issues is becoming a requirement for submitting grant applications to the Ethical, Legal, and Social Implications Program of the National Center for Human Genome Research at NIH . Dr. Straus said that a well written Informed Consent documen would indicate whether an effective informed consent would be obtained. Dr. Parkman expressed his reservation about separation of the process from the document in two sections. Dr. Secundy said that informed consent process can be described in a short statement.

Dr. Walters said that it is not feasible to do detailed editing around the table about the revision, and he suggested focusing on the specific amendments contained in the Part I-D-2 regarding the Informed Consent document for the present discussion. Dr. Parkman said that Part I-D-2-b-(9), *Explanation to Participants of the Specific Requirements of Gene Transfer Research*, furnishes the Principal Investigators specific information on how the participants should be informed. If specific language for each required element is not written, the investigators may not satisfactorily address these elements in their Informed Consent document. Dr. Zallen said that these specific languages can be provided by the OI on a list apart from the *Points to Consider*. Dr. Parkman suggested that questions in Part I-D-2-b-(9) should be prefaced with an explanation as to the necessity for the requested information.

Dr. Straus said that Part I-D-2-b-(3) regarding possible risk, discomfort, and side effects should be written more explicitly to inform patients about risks in gene transfer studies. Dr. Straus will provide a sentence fo this section. Dr. Secundy suggested inclusion of a statement to require the Informed Consent documer should be written in a language understandable to laypersons. Dr. Walters suggested to condense Part I-D-1 through I-D-1-a-(2), and to rearrange sections dealing with patient selection, privacy and confidentiality, and special issues. Drs. Zallen and Secundy said that questions contained in th sections are designed to ensure that no conflict of interest or coercion is involved in the informed consent process. Dr. Walters suggested to revise the Part I-D-1-a on communication of the study with potential participants in a procedural manner. Dr. DeLeon suggested to preface those questions in terms of why questions were asked.

The RAC recommended that the working group should develop a consolidated version of Part I-D, particularly Part I-D-2-b-(9), *Explanation to Participants of the Specific Requirements of Gene Transfer Research*, which includes language from both proposed documents. The RAC suggested that questions should be prefaced with an explanation as to the necessity for the requested information. Dr. Walters stated that since a broad consensus have been made on how to revise the informed consent section in Part I-D, the working group will be able to use these recommendations and submit a revised document to the next meeting.

XVIII. CONTINUATION OF THE RAC WORKING GROUP DISCUSSION ON ACCELERATED REVIEW - AMENDMENTS TO THE *NIH GUIDELIN* AND THE *POINTS TO CONSIDER*/DR. PARKMAN

Dr. Parkman presented an overview of the *Proposed Cover Sheet for Accelerated Review of Human Gene Transfer Experiments (Accelerated Review)*. The proposed cover sheet could be adopted as a preliminary mechanism for screening human gene transfer studies that may qualify for the accelerated

review process previously approved by the RAC. Principal Investigators requesting consideration of their protocol for the *Accelerated Review* process must complete the cover sheet. Based on the information provided by the Principal Investigator, NIH / ORDA in consultation with the RAC Chair and one or m RAC members, as necessary, will make a determination regarding eligibility for *Accelerated Review*. In the event that a protocol is denied review by this accelerated process, the proposal will be reviewed by the full RAC.

Dr. Smith said that the text on the proposed definition of the category on "umbrella" protocols need to be clarified. The category is not intended for a Principal Investigator to initiate a new study at multiple sites without a major review. Ms. Wilson explained that the definition applies to protocols in which the Principal Investigators indicated in their submission that the studies will be performed at multiple sites. Dr. Smith asked whether the initial review will be a *Major Action*. Dr. Parkman said that the initial review is a *Major Action*. Ms. Grossman asked whether the multicenter trial proposed by Vical , Inc., San Diego, Calif that is based on a protocol previously approved for other Principal Investigators will be included in this category. Dr. Parkman explained that this trial involves different study designs at many sites and is not a typical "umbrella" protocol. For reviewing an "umbrella" protocol, the master protocol will receive a major review and will be considered a *Major Action* when first submitted. When the Principal Investigator requests inclusion of additional sites, these modifications will be reviewed as a *Minor Action*. Ms. Grossman asked whether this category would include a protocol wherein a new Principal Investigator intends to perform a previously approved protocol at additional sites. Dr. Parkman said that if nothing substantially new is proposed, it could qualify as a *Minor Action*. Dr. Walters asked if the "umbrella" protocols differ from other categories involving new Principal Investigators and new sites. Dr. Parkman cited as a best example of the "umbrella" protocol would be the study of brain tumor treatment with herpes simplex virus thymidine kinase / Ganciclovir in which standard virus producer cells will be supplie central laboratory for administration to patients at multiple sites. Dr. Parkman said that the "umbrella" category is new and that no protocols have been proposed for RAC review. Dr. Parkman noted that there is no big difference from other categories dealing with new sites and new Principal Investigators, but he envisioned that repeated submission of new protocol documents will not be needed in this "umbrella" category.

Dr. Straus asked to clarify the definition of the Category 3 on new site/original Principal Investigator. Dr. DeLeon said that this category will be for a Principal Investigator to transfer a RAC-approved protocol t new site. Dr. Zallen asked whether this request will be a minor modification. Dr. Wivel remarked t minor modification is also a *Minor Action* similar to *Accelerated Review*. Dr. Parkman explained that the reason to create this category for *Accelerated Review* is that transfer of a protocol to a new site sometimes will involve additional issues such as new laboratory expertise and new personnel. These new issues will be reviewed with a new protocol submission. Dr. Straus stated his understanding that Category 4, new site/new Principal Investigator, will be for a Principal Investigator who wishes to initiate a protocol previously approved by the RAC at a new site, and Category 3, new site/original Principal Investigator, will be for a Principal Investigator to take his or her own RAC-approved protocol to a new site.

Dr. Post suggested that Dr. Parkman and the ORDA develop the final language to define thes categories. Dr. Motulsky concurre

Dr. Parkman introduced the checklist to be submitted by the Principal Investigators with their protocols for *Accelerated Review*. The purpose of the checklist is to have the Principal Investigators answer the pertinent questions in order to aid the ORDA staff in determining eligibility fo *Accelerated Review*. The checklist is very similar to the one approved for the single-patient *Expedited Review* except for item B-11. Item B-11 asks the question whether the vector has been reviewed and approved for clinical investigation by the Food and Drug Administration. It is certain that the vector will be available for single-patient

expedited trial, and the question is not relevant for the present *Accelerated Review*. Dr. Parkman suggested the deletion of this item from the proposed check list.

Ms. Grossman asked to clarify item C-4 on the question of whether the proposed study is similar to another RAC-approved protocol. The Principal Investigator needs to identify the major differences in the checklist.

Dr. Secundy asked for clarification of item E dealing with the Informed Consent document. Dr. Parkma explained that these listed elements for Informed Consent are frequently overlooked by the Principal Investigators, and the listing is to assure that the Principal Investigators have included these elements. Dr. Parkman said that submission for *Accelerated Review* should be a complete document similar to that required for regular review including an IRB -approved Informed Consent document, *Points to Consider*, etc. Drs. Straus and Zallen agreed with Dr. Parkman that a listing of required Informed Consent eleme will aid the ORDA staff in determining whether all important questions have been addressed by th Principal Investigators in their Informed Consent. Dr. Secundy noted that the language should be clarif to indicate that these elements are essential but not the only required elements for the Informed Consent document. Dr. Straus said that these additional elements are already incorporated into the revised *Points to Consider*. Dr. Parkman explained that the purpose of highlighting these elements is to aid ORDA sta in determining whether they are addressed by the Principal Investigators. Dr. Straus suggested language to ask Principal Investigators to provide a copy of the IRB -approved Informed Consent document consistent with the *Points to Consider*, and to underline the text addressing the listed specific items. Dr. Zallen remarked that there are circumstances in which a particular element is not appropriate for inclus in a particular Informed Consent document. She cited an example where the Principal Investigators might avoid mentioning an autopsy in the Informed Consent document to be prepared for children. Dr. Zallen said that if a particular item is not addressed in the Informed Consent document, the Principal Investigators should provide an explanation as to the reason for its omission.

The RAC approved a motion made by Dr. Parkman and seconded by Dr. Secundy to accept the propo cover sheet with the incorporation of minor modifications by a vote of 13 in favor, 0 opposed, and no abstentions. The current document will be divided into 2 separate documents: (1) *Accelerated Review* cover sheet, and the (2) *Cover Sheet for Expedited Review of a Single Patient Human Gene Transfer Experiment (Expedited Review)*. The difference between these two documents is that the *Expedited Review* cover sheet will include the following addition questions: "Has the vector been reviewed and accepted for clinical investigation by the FDA? What was the date of IND submission? Is there a suffici supply of the clinical grade material available to complete the proposed study? If clinical grade material is unavailable, on what date will such material become available?" These additional questions that will be incorporated into the *Expedited Review* cover sheet will be included as item number 11 under Section B, *Vector, Target Cell, and Transduction Procedures*.

The RAC-approved version of the *Accelerated Review* cover sheet reads:

PROPOSED COVER SHEET FOR ACCELERATED REVIEW OF A HUMAN GENE TRANSFER EXPERIMENT

A. BACKGROUND

1. Provide the following information about the proposed study: title, principal investigators, and participating institutions.

B. VECTOR, TARGET CELL, AND TRANSDUCTION PROCEDURES

1. What are the proposed gene and vector for this protocol?

2. Has the proposed vector previously been approved by the RAC? If so, provide the title and principal investigator(s) of at least one RAC-approved protocol utilizing this vector. If not, attach the complet vector sequence (hard copy and a 3½ inch diskette in ASCII format).

3. Who is the vector supplier?

4. What is the target cell to be transduced by the proposed vecto

5. What is the rate of transduction of the proposed vector and target cells in the proposed setting (i.e., your laboratory)?

6. What is the level of gene expression demonstrated in the target cell?

7. How was gene expression determined?

8. What assay was used to detect replication-competent virus (RCR

9. Was RCR detecte

10. What is the level of sensitivity of the RCR assay? (Attach documentation

C. CLINICAL PROTOCOL

1. What *in vitro* or *in vivo* system(s) were used to determine preclinical efficac

2. What is the end point of the protocol?

3. Is the proposed study *identical* to another RAC-approved protocol except that the study will be performed at a satellite institution? If so, provide a letter of cross-reference from the sponsoring institution.

4. Is the proposed study *similar* to another RAC-approved protocol? Identify the major differences.

D. LOCAL COMMITTEE APPROVALS

1. Has the proposed study been *unconditionally* approved by your Institutional Biosafety Committee? If so, provide a copy of the approval.

2. Has the proposed study been *unconditionally* approved by your Institutional Review Board? If so, provide a copy of the approval.

E. INFORMED CONSENT DOCUMENT

1. Provide a copy of the IRB -approved Informed Consent document, consistent with the *Points to Consider*, and underline the text addressing the following specific items:

NOTE: If any of these items are not addressed in the Informed Consent document, provide an explanation as to the reason for their omission.

a. Any requirement for use of birth-control by male and female participants during the course of the experiment;

b. Financial costs for which the individual research subject will be responsible;

c. Need for long-term follow-up and the arrangements for such follow-up;

d. Statement indicating that a request for permission to perform an autopsy will be made of the family, regardless of the immediate cause of death;

e. Arrangements in place at the research institution for sharing information with the new media and the public;

f. Provisions for protecting patient privacy and the confidentiality of data obtained from individual participants in the research.

F. ADDITIONAL INFORMATION

1. Provide curricula vitae (2 page Biosketch format) for principal investigators and key personne

2. Provide relevant publications only.

The RAC-approved version of the *Cover Sheet for Expedited Review of a Single Patient Human Gene Transfer Experiment (Expedited Review)* cover sheet reads:

COVER SHEET FOR EXPEDITED REVIEW
OF A SINGLE PATIENT HUMAN GENE TRANSFER EXPERIMENT
(Expedited Review)
A. BACKGROUND

1. Provide the following information about the proposed study: title, principal investigators, and participating institutions.

B. VECTOR, TARGET CELL, AND TRANSDUCTION PROCEDURES

1. What are the proposed gene and vector for this protocol?

2. Has the proposed vector previously been approved by the RAC? If so, provide the title and principal investigator(s) of at least one RAC-approved protocol utilizing this vector. If not, attach the complet vector sequence (hard copy and a 3½ inch diskette in ASCII format).

3. Who is the vector supplier?

4. What is the target cell to be transduced by the proposed vecto

5. What is the rate of transduction of the proposed vector and target cells in the proposed setting (i.e., your laboratory)?

6. What is the level of gene expression demonstrated in the target cell?

7. How was gene expression determined?

8. What assay was used to detect replication-competent virus (RCR

9. Was RCR detecte

10. What is the level of sensitivity of the RCR assay? (Attach documentation

11. Has the vector been reviewed and accepted for clinical investigation by the Food and Drug Administration? What was the date of investigational new drug (IND) submission? Is there a sufficien supply of the clinical grade material available to complete the proposed study? If clinical grade material is unavailable, on what date will such material become available?

C. CLINICAL PROTOCOL

1. What *in vitro* or *in vivo* system(s) were used to determine preclinical efficac

2. What is the end point of the protocol?

3. Is the proposed study *identical* to another RAC-approved protocol except that the study will be performed at a satellite institution? If so, provide a letter of cross-reference from the sponsoring institution.

4. Is the proposed study *similar* to another RAC-approved protocol? Identify the major differences.