DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
December 2-3, 1993

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The Recombinant DNA Advisory Committee (RAC) was convened for its fifty-sixth meeting at 9:00 a.m. on December 2, 1993, 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:

Constance E. Brinckerhoff, Dartmouth Medical School
Ira H. Carmen, University of Illinois
Gary A. Chase, Johns Hopkins University
Patricia A. DeLeon, University of Delaware
Roy H. Doi, University of California, Davis
E. Peter Geiduschek, University of California, San Diego
Mariann Grossman, Hospital of the University of Pennsylvania
Robert Haselkorn, University of Chicago
Donald J. Krogstad, Tulane University School of Medicine
Brigid G. Leventhal, Johns Hopkins Hospital
Abbey S. Meyers, National Organization for Rare Disorders
A. Dusty Miller, Fred Hutchinson Cancer Research Center
Robertson Parkman, Childrens 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, VA 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:

Leon Baltrucki, NHLBI
Bobbi Bennett, OD
Steve Brody, NHLBI
Diane Bronzert, NCI
Sarah Carr, OD
Jan Casadei, NCI
Shan Chu, NHLBI
Claire Danel, NHLBI
F. William Dommel, OD
Tony Eissa, NHLBI
Gary Ellis, OD
Robert Fenton, NCI
Judy Fradkin, NIDDK
Maryellen Franko, NCI
Barry Goldspiel, NCI
Madelon Halula, NIAID
Jim Higginbotham, NHLBI
Christine Ireland, OD
Susan Jenks, NCI
Sachiko Kajigaya, NHLBI
Stefan Karlsson, NINDS
Dai Katayose, NHLBI
Masako Kawase, NHLBI
Becky Lawson, OD
Johnson Liu, NHLBI
Catherine McKeon, NIDDK
Koichi Miyamura, NHLBI
Richard Morgan, NCHGR
Eric Oshiro, NINDS
Joan Porter, OD
Zvi Ram, NINDS
Melissa Rosenfeld, NHLBI
Nava Sarver, NIAID
Prem Seth, NHLBI
Kyoichi Shibuya, NCI
Thomas Shih, OD
Mario Sznol, NCI
Dennis Taub, NCI

John Villa, NINDS
Margo Warren, NINDS
Debra Wilson, OD
Haiping Wu, NHLBI
Neal Young, NHLBI

Others:

Paul Aebersold, Food and Drug Administration
Robert Anderson, Food and Drug Administration
W. French Anderson, University of Southern California
Briget Binko, Cell Genesys, Inc.
Andrew Braun, Harvard University
G'dali Braverman, ActUp
Joe Bruder, GenVec, Inc.
George Buffleben, Public
Gracia Buffleben, Public
Jeffrey Carey, Genetic Therapy, Inc.
Rachel Carle, Genzyme Corporation
Mike Casey, Genetic Therapy, Inc.
Fred Chang, University of Michigan Medical Center
Henry Chang, Shared Medical Research Foundation
Jan Chapell, Genetic Therapy, Inc.
Seng Cheng, Genzyme Corporation
Yawen Chiang, Genetic Therapy, Inc.
Larry Couture, Genzyme Corporation
Ronald Crystal, New York Hospital/Cornell Medical Center
Aileen Deist, Genetic Therapy, Inc.
Anne Driscoll, Fox, Bennett, and Turner
Eli Embley, F-D-C Reports, Inc.
Habib Fakhrai, San Diego Cancer Research Institute
Susan Falen, Genetic Therapy, Inc.
Jeffrey Fox, ASM News and Biotechnology
Joyce Frey, Food and Drug Administration
Ray Frizzell, University of Alabama, Birmingham
Morgan Gale, Hearings-on-the-Line
Alan Goldhammer, Biotechnology Industry Organization
Scott Graham, University of Iowa
Adam Grossman, ProTravel International
Lisa Grossman, ProTravel International
Robert Grossman, ProTravel International
Richard Haubrich, University of California, San Diego Treatment Center
Douglas Hickman, T. Rowe Price
David Holzman, BioWorld
Tom Horiagon, Chimerix Corporation
Edie Irvine, Genetic Therapy, Inc.
Burkhard Jansen, University of Vienna
Jack Jaugstetter, Genentech, Inc.
Rachel King, Genetic Therapy, Inc.
Toshi Kotani, Genetic Therapy, Inc.

John Kovach, Mayo Clinic
Imre Kovesdi, GenVec, Inc.
Steven Kradjian, Vical, Inc.
John Krauss, University of Michigan Medical Center
James Logan, University of Alabama, Birmingham
Donald Longenecker, Viagene, Inc.
Stephen Lupton, Targeted Genetics Corporation
Dan Maneval, Canji, Inc.
Tony Marcel, TMC Development
Keith March, Genetic Therapy, Inc.
Steve Marcus, Genetic Therapy, Inc.
Alan McClelland, Genetic Therapy, Inc.
Gerard McGarrity, Genetic Therapy, Inc.
Duncan McVey, GenVec, Inc.
Bruce Merchant, Viagene, Inc.
Andra Miller, Food and Drug Administration
Karen Millison, Genetic Therapy, Inc.
Gaye Morgenthaler, Murenove, Inc.
Gary Nabel, University of Michigan
Jeffrey Ostrove, Microbiological Associates, Inc.
Joseph Palca, National Public Radio
Hubert Pehamburger, University of Vienna
Michael Pensiero, Genetic Therapy, Inc.
Anne Petruska, The Blue Sheet
Stephen Pijar, University of Maryland
Paul Recer, Associated Press
Thomas Reynolds, Targeted Genetics Corporation
Rex Rhein, Biotechnology Newswatch
Joseph Rokovich, Somatix, Inc.
Alan Schreiber, Vical, Inc.
Friedrich Schuening, Fred Hutchinson Cancer Research Center
Richard Scotland, Genzyme Corporation
G. Terry Sharrer, Smithsonian Institution
Tomiko Shimada, Ambience Awareness International
Juliette Singh, Baxter Health Care
Alan Smith, Genzyme Corporation
Robert Sobol, San Diego Cancer Research Institute
Eric Sorscher, University of Alabama, Birmingham
Judith St. George, Genzyme Corporation
Marcus Stern, Copley News Service
Nevin Summers, Ingenex, Inc.
Jennifer Sutton, Association of American Medical Colleges
Paul Tolstoshev, Genetic Therapy, Inc.
Bruce Trapnell, Genetic Therapy, Inc.
Cynthia Utley, GenVec, Inc.
Christine VandePol, Rhone Poulenc Rorer, Inc.
Samuel Wadsworth, Genzyme Corporation
Trish Waitschies, MD Anderson Cancer Center
John Warner, Viagene, Inc.
Michael Welsh, University of Iowa

Katie Whartenby, Food and Drug Administration
Chet Whitley, University of Minnesota
Tom Wickham, GenVec, Inc.
M. Douglas Winship, Curative Technologies, Inc.
Janet Woodcock, Food and Drug Administration
Joseph Zabner, University of Iowa
Gregory Zaic, Prince Ventures

I. CALL TO ORDER

Dr. Walters (Chair) called the meeting to order and stated that notice of the meeting was published in the *Federal Register* on November 9, 1993 (58 FR 59612), 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 (PIs). 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 stated that the number of human gene therapy protocols submitted for RAC review has rapidly increased over the last 3 years. He noted that 2 gene therapy trials were approved by the RAC in 1990, 3 trials in 1991, 10 trials in 1992, and 21 trials in the first 3 meetings of 1993. To date, the RAC has recommended approval of 36 human gene therapy trials to the NIH Director (does not include gene marking studies). (See Attachment II for complete protocol listing).

Dr. Walters stated that a favorable response was received to the RAC's recommendation regarding provision of medical care for subjects injured during the course of their participation in research. On August 6, 1993, Dr. Ruth Kirschstein, Acting NIH Director, responded to the RAC stating that she would forward the recommendations to Dr. Philip Lee, Assistant Secretary for Health, Department of Health and Human Services. In a letter dated October 8, 1993, Dr. Cliff Gaus (health care reform coordinator for Dr. Lee), indicated that the benefits package now envisioned for health care reform would probably cover services to subjects injured in clinical research. A brief discussion ensued about the interim policy regarding this issue.

Dr. Walters stated that the Office of Recombinant DNA Activities (ORDA) forwarded letters to two Institutional Review Boards (IRBs): (1) St. Jude's Children's Research Hospital to notify them of the RAC's recommendation to divide the Informed Consent document into two separate documents: a guardian consent form and a child's assent form (Dr. Kun's protocol). (2) University of California, San Diego (UCSD) to notify them of the RAC's requirement that prophylactic azidothymidine (AZT) administration be deleted from the protocol and that rabbit pyrogen testing not be mandatory (Dr. Wong-Staal's protocol). As a point of clarification, Dr. Parkman requested that the issue of AZT administration be verified.

II. MINUTES OF THE SEPTEMBER 9-10, 1993, RAC MEETING

Dr. Walters called on Dr. Carmen to review the minutes of the September 9-10, 1993, RAC meeting. Dr. Carmen summarized Dr. Hirano's written comments on the minutes and concurred that the minutes were an accurate reflection of the September meeting and recommended their approval. Minor changes were submitted by Drs. Miller and Zallen.
Committee Motion

The RAC approved a motion made by Dr. Carmen and seconded by Dr. Leventhal to accept the September 9-10 RAC minutes with the inclusion of minor changes by a vote of 15 in favor, 0 opposed, and no abstentions.

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

Dr. Walters stated that the RAC had approved minor modifications to the following RAC-approved human gene transfer protocols since the September 9-10, 1993, RAC meeting (See Attachment III for a complete list of minor modifications approved to date):

PROTOCOL	PRINCIPAL INVESTIGATOR	DATE APPROVED
9212-034	Ronald G. Crystal	October 8, 1992
9212-036	Michael J. Welsh	October 18, 1993
9209-030	Albert B. Deisseroth	November 3, 1993
9209-030	Albert B. Deisseroth	November 18, 1993
9212-034	Ronald G. Crystal	November 29, 1993
9206-019	Edward H. Oldfield	November 29, 1993

Dr. Walters noted that the only major concern in reviewing and approving these minor modifications was the addition of bronchial biopsies requested by Dr. Crystal. This procedure was not originally approved for this protocol; although other RAC-approved cystic fibrosis (CF) protocols include this procedure. After consultation with pulmonologists, Dr. Walters concluded that bronchial biopsy, as proposed for this protocol, poses less risk to patients than transbronchial biopsy.

IV. WORKING GROUP ON DATA MANAGEMENT - SEMI-ANNUAL DATA REPORT/DR. LEVENTHAL

Dr. Walters called on Dr. Leventhal to summarize the semi-annual data reports submitted by the PIs of NIH-approved human gene transfer protocols. Dr. Leventhal stated that some investigators failed to provide adequate responses to the questions regarding possible adverse effects and evidence of gene transfer. She recommended that the Working Group on Data Management should have an interim meeting to revise the reporting requirements.

A total of 150 patients have been accrued onto the 50 NIH Director-approved protocols to date. Of these 50 studies, 7 are closed, 20 have had no patient accrual to date, and 12 are pending approva by the Food and Drug Administration (FDA). Summarized below are the categories of human gene transfer protocols that have been approved by the RAC to date (See Attachment IV for complete data management report):

	Therapy	Marking	Total (T + M)
RAC Approved	35	23	58
NIH Director Approved	28	22	50
Categories of RAC-Approved Protocols			
Cancer	26	4	30
Cystic Fibrosis	4	1	5

SCID/ADA	1	0	1
Acute Hepatic Failure	0	1	1
Familial Hypercholesterolemia	1	0	1
Gaucher Disease	2	0	2
Bone Marrow Marking/Cancer	0	15	15
HIV(+)	2	2	4

The next review of human gene transfer data will be presented at the June 9-10, 1994, RAC meeting. Dr. Leventhal noted several issues that should be addressed by the working group prior to the June 1994 data reporting period. PIs should not be required to submit semi-annual data reports as a follow-up to protocols that have been closed for >1 year. She stated concern about the issue of under- and over-accrual of patients intoNIH-approved protocols. Another issue is the lack of reporting unexpected toxicity and adverse reactions. Any such observation should be reported to the RAC, particularly in light of recent severe adverse reactions encountered in the fialuridine, or FIAU, hepatitis drug trial atNIH. Dr. Janet Woodcock of the FDA stated that the FDA requires that any unexpected adverse reaction must be reported immediately. All events, expected or unexpected, are reported annually and at the close of each study. Dr.Leventhal suggested that PIs submit copies of FDA adverse reaction reports to the RAC.

Discussion ensued regarding recent press reports and public expectations about human gene therapy and the current state of art of this new biotechnology. The majority of the human gene transfer trials that have been approved are Phase I/II studies; therefore, the trials are not designed to assess efficacy. These Phase I/II studies should be evaluated on the basis of whether proposed scientific objectives have been obtained.

V. UPDATE ON THE OLDFIELD PROTOCOL ENTITLED: *GENE THERAPY FOR THE TREATMENT OF BRAIN TUMORS USING INTRA- TUMORAL TRANSDUCTION WITH THE THYMIDINE KINASE GENE AND INTRAVENOUS GANCICLOVIR (#9206-019)/DR. RAM*

Dr. Walters called on Dr. Zvi Ram of the NIH, Bethesda, Maryland, to provide an update on this human gene transfer protocol. Dr. Ram stated that as previously reported to the RAC, patient #1 developed a secondary brain tumor following injection of vector producing cells (VPC) and subsequent administration of ganciclovir. Some RAC members were initially concerned that this secondary tumor may have been related to the gene transfer procedure. The first brain tumor was diagnosed as an anaplastic renal cell metastasis. When the patient developed aglioblastoma at a site distant from the original tumor subsequent to gene transfer, extensive analyses were performed. Molecular analysis demonstrated no evidence of the retroviral vector or theVPC in the second tumor (glioblastoma). Patient #1 demonstrated progressive disease that led to death. Extensive post-mortem studies were conducted, and subsequent analyses demonstrated that the first brain tumor was misdiagnosed. The original brain mass was not a renal cell carcinoma metastasis, but a primaryglioblastoma. Patient #1 had two primary tumors, a renal cell carcinoma and a glioblastoma. Subsequent progression of the glioblastoma resulted in the patient's death. Dr. Leventhal noted that she reviewed the data submitted by the investigators and concurs with this assessment.

VI. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: INTRATHECAL GENE THERAPY FOR THE TREATMENT OF LEPTOMENINGEAL CARCINOMATOSIS/DRS. OLDFIELD AND RAM*

Review--Dr. Smith

Dr. Walters called on Dr. Smith to present his primary review of the protocol submitted by Drs. Edward H. Oldfield and Zvi Ram of NIH, Bethesda, Maryland. Dr. Smith stated that the PIs propose to use the herpes simplex virus thymidine kinase (HSV-tk) gene/ganciclovir (GCV) strategy that has been previously approved by the RAC for other malignancies. Leptomeningeal carcinomatosis is a fatal disease; therefore, a probable candidate for gene transfer research. The proposed vector, G1TK1SvNa, is similar to the previously approved construct. The packaging cell line, PA317, has been approved previously. A total of 20 patients will be entered into the study. Patients will receive intraventricular and/or intrathecal injections of VPC. The end points of the study are to: (1) assess toxicity (i.e., cerebral spinal fluid (CSF) meningitis symptoms and/or obstruction induced by placing up to 8 x 109 VPC cells in 120 ml of CSF, and any adverse reactions such as the asymptomatic gliosis encountered in the previous trial; (2) determine the kinetics and distribution of the VPC following injection into the CSF and CSF vector titer; and (3) determine clinical efficacy as assessed by standard tumor cell markers and magnetic resonance imaging (MRI).

Dr. Smith expressed concern about the asymptomatic gliosis that was encountered in the investigators' previous brain tumor protocol. He asked the PI to summarize the most recent data regarding this observation and any correlations with the proposed study. The number of VPC proposed for this study is greater than the number of VPC used for the rhesus monkey studies. This larger number of cells may increase the risk of CSF blockade and other meningeal complications. The -galactosidase reporter gene was used successfully as a marker to assess gene transfer in the preclinical studies; therefore, this reporter gene should yield valuable information about HSV-tk transduction of tumor cells in the CSF in the human trial. He asked the investigators whether there is any data demonstrating efficacy of HSV-tk gene transfer and GCV administration on breast and lung tumor cells. He concluded that most of his initial concerns were adequately addressed, and recommended approval of the protocol.

Review--Dr. Brinckerhoff

Dr. Brinckerhoff said that the proposed study is clearly described and thoroughly documented. This protocol is a direct extension of previously approved HSV-tk/GCV brain tumor studies. Clinical efficacy has been demonstrated in the rat model. Of the 8 patients treated on Dr Oldfield's glioblastoma protocol, 5 have demonstrated an antitumor response. Injection of the VPC and subsequent GCV administration has been well tolerated in all patients; this observation lends strong support for the present proposal. Dr. Brinckerhoff posed the following questions. Does the transduction of dividing cells in the subarachnoid space include macrophages and epithelial cells as well as tumor cells? Are the VPC capable of passing out of the central nervous system, circulating in the blood, and eliciting an immune response? Are there possible cryptic transcription start sites in the vector construct? She concluded that the proposed study could potentially prolong survival of these patients by a relatively non-invasive means and may serve as a paradigm for future gene therapy protocols; therefore, the RAC should recommend approval.

Other Comments

Dr. Leventhal asked whether the proposed number of patients is sufficient to evaluate efficacy. Dr. Ram responded that this study is not designed to evaluate efficacy. The total number of patients will be divided into 4 dose-escalation groups.

Investigator Response--Dr. Ram

Dr. Ram summarized the results obtained from Dr. Oldfield's previously approved glioblastoma protocol which is analogous to this study. Twelve patients (10 surgically inaccessible and 2 surgically accessible) have received HSV-tk/ganciclovir administration. In the surgically accessible group, patients' tumors were resected 1 week following VPC injection and subsequently analyzed for *in vivo* evidence of gene transfer. The objectives of the study (i.e., safety, antitumor response, and *in vivo* gene transfer) were achieved and there has been no evidence of immediate or delayed toxicity. Although the study was not designed to be curative, significant antitumor responses have been demonstrated. A subgroup of patients demonstrated no evidence of antitumor activity, and their tumors rapidly progressed for undetermined reasons. Preliminary *in situ* hybridization assays of resected tumors indicate successful gene transfer into tumor cells at the VPC injection site.

Dr. Miller remarked that these glioblastoma patients have a limited life expectancy which precludes any observation of long-term safety. Dr. Ram emphasized that the proposed leptomeningeal carcinomatosis study will yield valuable scientific information for a uniformly fatal disease. CSF circulates around the brain and spinal cord and comes in contact with every cell of the leptomeninges. Injection of VPC into this space will yield important information about the pharmacodynamics of GCV and distribution of the VPC and vector. Such data will be valuable for future gene therapy applications.

Dr. Haselkorn asked if tumor markers exist that would allow the investigators to distinguish between responding and non-responding tumors. Dr. Ram answered that although a few markers exist for glioblastoma, there are no known markers for leptomeningeal carcinomatosis. Dr. Doi asked if experiments had been performed to look for the presence of the HSV-tk gene in those patients who exhibited rapidly growing tumors. Dr. Ram responded that the biology of the tumor often changes after several resections. Dr. Miller stated that evidence of antitumor response justifies the expansion of this treatment to other diseases.

To follow up on Dr. Doi's question, Ms. Grossman questioned whether the HSV-tk gene sequences were detected in the non-responding tumor group. Dr. Ram answered that *in situ* hybridization assays were performed only on resected tumor specimens obtained from the surgically accessible group. Such analysis may be inconclusive since the specimens were obtained 7 days after GCV treatment which eliminates the HSV-tk transduced cells.

Dr. Parkman asked how the dynamics and distribution of VPC will be assessed. Will tumors block the ventricular system and the subarachnoid space? Dr. Ram replied that one of the exclusion criterion of the proposed study is evidence of such a blockage. CSF samples will be obtained from the ventricular system and from the lumbar spinal cord to monitor the dynamics and distribution of the vector and VPC. Dr. Ram noted that *in vivo* monkey experiments demonstrated even distribution of the vector and VPC between the cervical and lumbar spinal cord.

Dr. Miller asked why post-mortem studies were not performed on most of the glioblastoma patients. Dr. Ram explained that it is often difficult to obtain permission from relatives, etc., to obtain post-mortem brain tissue. Dr. Leventhal acknowledged that such permission is often difficult to obtain.

Committee Motion

A motion was made by Dr. Smith and seconded by Dr. Secundy to approve the protocol. The motion passed by a vote of 13 in favor, 1 opposed, and 1 abstention.

VII. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: RETROVIRAL MEDIATED GENE TRANSFER OF THE FANCONI ANEMIA COMPLEMENTATION GROUP C GENE TO HEMATOPOIETIC PROGENITORS OF GROUP C PATIENTS/DRS. LIU AND YOUNG*

Review--Dr. Parkman

Dr. Walters called on Dr. Parkman to present his primary review of the protocol submitted by Drs. Johnson M. Liu and Neal S. Young of NIH, Bethesda, Maryland. Dr. Parkman stated that Fanconi anemia is an autosomal recessive genetic disease in which the affected individuals have an inability to repair spontaneous or induced DNA breaks. As a consequence of their decreased capacity to repair DNA breaks, patients develop aplastic anemia, have an increased likelihood of cancer development, and may have anatomic abnormalities involving the skeleton and kidney. Four complementation groups of Fanconi anemia have been defined. The gene responsible for the defect, Fanconi anemia complementation C (FACC) has been identified and cloned. The protein product of FACC is 63 kd; however, the function of this protein is unknown. The investigators have demonstrated that *in vitro* transduction of the FACC gene into patients' cells (B lymphoblast cell lines and target CD34(+) cells) results in the normalization of the sensitivity of the transduced cells to mitomycin C treatment and a reduction in the number of induced chromosomal breaks. The investigators have demonstrated in this preclinical model that transduction of abnormal cells with the FACC gene can result in the physiological normalization of these cells. The proposed study is similar to the Gaucher's disease protocols previously approved by the RAC in that CD34(+) cells will be isolated from peripheral blood following granulocyte colony stimulating factor (G-CSF) stimulation. The use of peripheral blood cells eliminates the possible risk associated with the use of general anesthesia for bone marrow harvesting. Questions still exist about the relative quality and frequency of obtaining true pluripotent hematopoietic stem cells from peripheral blood versus bone marrow cells. Considering the risks of general anesthesia, the present approach is appropriate for the proposed study. CD34(+) cells will be isolated using the CellPro® monoclonal antibody column and transduced *in vitro* with the retroviral vector in the presence of the growth factors, interleukin-3 (IL-3), interleukin-6 (IL-6), and G-CSF. The cells will be reinfused into patients following transduction. Patients will receive a maximum of 4 infusions over a period of 12 months, at a frequency of every 2 months. Peripheral blood and bone marrow cells will be analyzed for the presence of the transduced FACC gene and its functional effect of conferring resistance to mitomycin C. This protocol is a logical extension of the investigators' previous work on Gaucher's disease and the Autologous Bone Marrow Transplant Program at NIH. If a significant *in vivo* selective growth advantage is demonstrated for the transduced stem cells and their progeny, this study may result in a potential clinical benefit. The investigators have adequately responded to most of the issues raised in the primary review.

Review--Dr. Smith

Dr. Smith stated that although the investigators partially responded to some of the questions posed in his written comments, there are several issues that require further discussion. One major concern is the use of growth factors both in patients and during the transduction procedure. CD34(+) cells will be harvested following mobilization with G-CSF. In patients with non-Fanconi's myelodysplastic syndromes, growth-factor administration can result in elevated blast counts, presenting the theoretical risk of accelerating progression to acute leukemia. Similarly, *ex vivo*

treatment of the harvested progenitor cells with a cocktail of experimental growth factors (IL-3, G-CSF, and IL-6) carries a similar risk of increasing the susceptibility of an abnormal stem cell becoming leukemic or furthering the growth potential of an already extantleukemic cell clone. This theoretical risk is not adequately described in the protocol. The investigators have not stated clearly that the proposed treatment only attempts to correct thehematopoietic cells, not other cells that are affected by this disease. The investigators have only provided short-term tissue culture data. Dr. Smith posed the following questions. What are the long-term effects of inserting the FACC gene under constitutive expression conditions that alter normal cellular function? Will the transduced cells be selected in G418? Can adequate numbers of CD34(+) cells be harvested from these aplastic patients? There is little information available about how the gene defect actually results in disease. Fanconi anemia is an appropriate candidate for gene transfer experiments and the investigators are well qualified to conduct such experiments; however, these issues must be addressed before the RAC makes a recommendation regarding approval.

Review--Dr. Carmen

Dr. Carmen stated that since the RAC has never reviewed any human gene transfer proposal for the treatment of the genetic diseaseFanconi anemia, the RAC should provide a careful review of this novel approach. The investigators have not provided data in an appropriate animal model, citing the fact that the exact biochemical function of theFACC gene is unknown. The protocol currently states that the PIs are "currently investigating the effect of long-term expression of the gene in a murine transplantation model." Ordinarily, recommending approval of a protocol that does not include a preclinical animal model is unusual, especially since patients will be 18 years o age. However, the investigators have provided adequate human *ex vivo* data to support the proposed study. Lymphoblast cell lines and CD34(+) cells isolated fromFanconi anemia patients were restored to their normal sensitivity tomitomycin C treatment following transduction with the FACC retroviral vector. He recommended modifications to the Informed Consent document that would make the language more understandable to laypersons and recommended approval of the protocol contingent on the acceptance of the modified Informed Consent document language.

Other Comments

Dr. Post expressed concern about the possible overproduction of the FACC protein, which has an unknown function in hematopoietic cells. He asked the investigators to provide additional information about the murine transplantation experiment that was conducted to determine the constitutive expression of the FACC gene.

Investigator Response--Dr. Liu

In response to Dr. Smith's concern about the use of growth factors inFanconi anemia patients, Dr. Liu said that G-CSF has been used previously to treat several Fanconi anemia patients with severe pancytopenia for up to 1 year. One patient demonstrated a spontaneousclonal karyotypic abnormality prior to G-CSF treatment. To date, there is no evidence that treatment ofFanconi anemia patients with G-CSF poses the risk of conversion from preleukemic to a leukemic state. Dr. Liu acknowledged that there is a theoretical concern about leukemic conversion which led the PIs to limit the administration of G-CSF to a 1 week period. Patients will be placed under close observation for this potential risk. Drs. Smith andDoi expressed concern that patients will be included who have clonal karyotypic abnormalities of their blood cells. Dr. Liu responded that retrospective studies of Fanconi anemia patients suggest that there is no association ofclonal karyotypic abnormalities with the onset of leukemia.Fanconi anemia is a very rare genetic

disease, which places severe limitations on the eligibility criteria. In response to Dr. Smith's question regarding the use of growth factors during the *ex vivo* transduction procedure, Dr. Liu stated that these procedures are designed to stimulate hematopoietic progenitor cells to divide in order to enhance transduction efficiency. There is very limited experience to indicate whether these factors are necessary for transduction of cells from Fanconi anemia patients. Dr. Smith was concerned that growth factors such as IL-6, IL-3, and G-CSF could result in the outgrowth of preleukemic cells during the transduction procedure. Dr. Liu explained that these growth factors have been used previously to treat patients who either are preleukemic or leukemic. There is no data indicating that these patients are at high risk of accelerating leukemia development. Dr. Post remarked that Dr. Cynthia Dunbar's semi-annual data report form (RAC protocol #9206-025) indicated that recent data suggests the possibility that G-CSF may favor the growth of leukemic versus normal progenitors during the *ex vivo* culture. Dr. Post agreed with Dr. Smith's concern about the use of growth factors during the transduction of cells from Fanconi anemia patients. Dr. Young, co-PI on the proposed study, responded that the *in vitro* data demonstrating leukemia cell proliferations by G-CSF or GM-CSF (granulocyte-macrophage colony stimulating factor) involved cells obtained from patients with acute or chronic myelogenous leukemia. This proposal involves Fanconi anemia patients, not myelogenous leukemia patients. Dr. Young stated that it is unreasonable to exclude the use of growth factors based on *in vitro* observations. Dr. Smith suggested that the investigators should contact Dr. Dunbar and request additional data regarding her observations.

In response to Dr. Post's question about murine transplantation experiments, Dr. Liu stated that these studies are ongoing. Bone marrow was obtained from C57/Bl6 mice and transduced with the FACC vector. These transduced cells were then reinfused into recipient W/Wv mice. Preliminary data indicate successful engraftment and transduction of the FACC gene into the stem cells of recipient mice. No abnormalities have been observed by necropsy of one recipient. Data are currently unavailable with regard to *in vivo* expression or transduction efficiency of the FACC gene. Ms. Grossman expressed her reservations about the lack of data derived from a relevant animal model. Dr. Miller remarked that the murine model will be useful to address many of the safety issues that have been posed by the RAC. If the transduced FACC gene is adequately expressed in mice, concerns about untoward effects of the FACC gene on normal cells can be addressed. Dr. Liu said that the suggested *in vivo* studies are in progress.

Committee Motion #1

A motion was made by Ms. Grossman and seconded by Dr. Secundy to defer the protocol based on the lack of *in vivo* data. Dr. Walters invited discussion on this motion. Dr. Post said that although the ongoing murine studies will address several safety issues, the data are incomplete. Dr. Post urged the investigators to further characterize the ongoing experiments in order to demonstrate the safety of FACC gene expression in mice.

Ms. Meyers commented that Fanconi anemia is a very rare disease, and little is known as compared to other more common genetic disorders. She expressed concern that there may never be an adequate amount of data to address all the RAC's concerns. She suggested that a more appropriate motion would be to approve the protocol contingent upon receipt of data derived from ongoing animal studies.

Dr. Parkman expressed concern that approval of this protocol, which involves gene transfer for the treatment of a genetic disease that has not been previously reviewed by the RAC, would set a precedent for other novel protocols. Although the investigators have submitted efficacy data

based on an *in vitro* model, little is known about the safety of long-term expression of the FACC gene in hematopoietic stem cells. Dr. Parkman noted that similar murine experiments were not required for RAC approval of other protocols, such as the adenosine deaminase (ADA)-deficiency protocol which also involved stem cell transduction.

Dr. Smith stated he is in favor of approving the protocol contingent on the submission of the additional data noted by Dr. Dunbar and review and approval of data obtained from the ongoing murine experiments. Dr. Post stated his view that the protocol should be deferred until the investigators return to the full RAC with the additional safety data. Dr. Miller stated that the protocol should be approved contingent on the submission of data from ongoing experiments; and recommended a 4 month follow-up for toxicity experiments would be adequate. Dr. Liu responded that 8 mice have been followed for a period of 3 months.

Dr. Walters asked Dr. Miller if he would like to offer a substitute motion for the original deferral motion made by Ms. Grossman.

Committee Motion #2

A substitute motion was made by Dr. Miller and seconded by Dr.DeLeon to conditionally approve this protocol contingent upon the receipt of the murine safety data to be reviewed by a subcommittee that includes the primary reviewers. Dr. Miller said that this motion will not delay initiation of the protocol. The RAC voted to accept Dr. Miller's substitute motion by a vote of 9 in favor, 6 opposed, and no abstentions.

Dr. Leventhal expressed her reservation about allowing a subcommittee to review the requested data. The RAC meets every 3 months; therefore, there is no reason that the investigators cannot present data derived from the ongoing studies at the next RAC meeting. Dr. Smith agreed that full RAC review would afford a more detailed examination of the data. Ms. Grossman stated her preference to defer approval of the protocol until the next meeting. Dr. Chase stated that the scientific review of these data could be adequately addressed by a subcommittee. Dr.Secundy disagreed with Dr. Chase's comments noting that public members offer valuable contributions to such reviews.

Dr. Doi suggested that the RAC should specify their recommendations to the investigators. Dr. Miller said that the mice involved in the ongoing toxicity studies should be observed for a period o 4 months based on the fact that this length of time is required to evaluate engraftment of transduced stem cells in mice. Dr. Smith said that in addition to the animal data, the RAC should have access to Dr. Dunbar's data demonstrating the effect of growth factors on the *ex vivo* transduction of stem cells. Dr. Liu asked if he would be required to submit the additional data 8 weeks prior to the next RAC meeting and whether resubmission of the entire protocol would be mandatory.

Dr. Secundy suggested that the Informed Consent document should be amended to include bone marrow examination as a condition for continuation in the protocol. Ms. Grossman, Drs. Parkman, Leventhal, and Zallen all stated that bone marrow examination with each reinfusion cycle should be an inclusion criterion in order to obtain scientifically meaningful data. Dr. Liu agreed to include this requirement in the protocol and in the Informed Consent document.

Dr. Walters called for a vote on the motion to conditionally approve the protocol contingent on the review of data derived from ongoing safety experiments by a subcommittee of the RAC. The

motion was defeated by a vote of 5 in favor, 10 opposed, and 1 abstention. Dr. Parkman suggested that a new motion should waive the 8 week deadline for submission and allow the investigators to resubmit the protocol up to 4 weeks prior to the next RAC meeting.

Committee Motion #3

A motion was made by Dr. Miller and seconded by Dr. Secundy to defer approval of the protocol until the investigators return to the full RAC with the following: (1) murine data demonstrating *in vivo* expression of the FACC gene and safety data accumulated over a period of 4 months demonstrating that the FACC-transduced cells do not result in any untoward effects; (2) data as cited in Dr. Cynthia Dunbar's semi-annual data report (RAC protocol # 9206-025) regarding the possibility that "stem cell factor could favor the growth of leukemic versus normal progenitors during *ex vivo* culture periods;" and (3) revisions to both the protocol and Informed Consent document to modify the eligibility criteria regarding the necessity for bone marrow examination following each reinfusion.

The consensus of the RAC was that the investigators are not required to submit this additional data until 4 weeks prior to the RAC meeting at which time the information will be reviewed. Submission of previously reviewed information is not required. The motion to defer approval of the protocol pending full RAC review of additional data passed by a vote of 14 in favor, 0 opposed, and 3 abstentions.

VIII. CONTINUATION OF DISCUSSION REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED: *A PHASE I CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFECTS IN HIV-1 INFECTED HUMANS OF AUTOLOGOUS LYMPHOCYTES TRANSDUCED WITH A RIBOZYME THAT CLEAVES HIV-1 RNA/DR. WONG-STAAL (SEE PREVIOUS DISCUSSION UNDER CALL TO ORDER)*

Dr. Parkman noted that the approval of Dr. Wong-Staal's human gene transfer protocol was contingent on the University of California, San Diego IRB eliminating the requirement for mandatory AZT administration. The transcripts of the September 9-10 meeting were reviewed, and this contingency was verified. ORDA noted that a letter of response has not yet been received from Dr. Wong-Staal's IRB.

IX. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED* : *INJECTION OF COLON CARCINOMA PATIENTS WITH AUTOLOGOUS IRRADIATED TUMOR CELLS AND FIBROBLASTS GENETICALLY MODIFIED TO SECRETE INTERLEUKIN-2/DRS. SOBOL AND ROYSTON*

Review--Dr. Miller

Dr. Walters called on Dr. Miller to present his primary review of the protocol submitted by Drs. Robert E. Sobol and Ivor Royston of the San Diego Regional Cancer Center, San Diego, California.

Dr. Miller explained that this Phase I study involves the injection of a mixture of autologous irradiated tumor cells and autologous irradiated IL-2-producing fibroblasts to stimulate antitumor immune responses in colon carcinoma patients. The fibroblasts will be engineered to produce IL-2 by using a replication-defective retroviral vector similar to other vectors that have been approved previously by the RAC. The proposal is well designed and addresses most issues related to the use of recombinant DNA in humans. The investigators have submitted preclinical data derived

from the CT26 BALB/c colorectal carcinoma murine model.

Dr. Miller stated that the data does not entirely support the protocol, especially regarding the generation of systemic antitumor immunity. Although immunity was observed at a concentration of 100 units of IL-2/24 hours, antitumor immunity was not demonstrated at doses up to 1,700 units of IL-2/24 hours. The animal model is irrelevant because the murine studies employed non-irradiated IL-2-secreting fibroblasts. The human study involves irradiated IL-2-secreting fibroblasts. Have experiments been conducted with animals that have established tumors? Why is there low viability when the IL-2 secreting fibroblasts are irradiated at 3,000 rads? He stated that if these concerns are adequately addressed by the investigators, the protocol should be approved on the basis that generation of antitumor immune responses may hold promise for the treatment of human cancers, and the use of irradiated cells presents minimal risk to the patients.

Review--Dr. Straus

Dr. Straus agreed with Dr. Miller's assessment about the minimal risk associated with the proposed study. Dr. Straus noted several initial concerns about the protocol, some of which were partially addressed by the PI's written responses. Dr. Straus expressed concern that the proposed vector is not identical to the previously approved vector, and safety data on the retrovirus lots has not been submitted. The protocol states that the fibroblasts and tumor cells will be lethally irradiated, yet data demonstrating the level of irradiation required for complete cell killing has not been provided. The investigators have not specified the exact treatment schedule or the number of patients they propose to enroll on the study. *In vivo* evidence of an antitumor response has not been demonstrated in animals with established disease. The Informed Consent document is exceedingly brief and many items, including the number and amount of blood drawings and possible side effects, have been omitted. Dr. Straus concluded that the protocol in its present form should not be approved.

Review--Dr. Zallen

Dr. Zallen stated that the nontechnical abstract is unacceptable because the language is not comprehensible to the laypersons. She stated that her concerns focus on 3 areas: (1) inadequate animal model studies, (2) the capability of the investigators to conduct the proposed experiment, and (3) the Informed Consent document. She noted that her initial concern about the use of the term "immunization" in the Informed Consent document has been corrected in the revised document. The *Risks and Discomforts Section* of the Informed Consent document does not adequately describe the possible allergic reactions and risks associated with replication-competent retroviruses (RCR). The statement in the Informed Consent document about financial responsibility of research costs to the patients is unacceptable. This document should clearly state that neither the patients nor their insurance companies are responsible for any of the direct costs arising from their participation in this study. In regard to preclinical data, the investigators should clarify the results obtained in the animal model, e.g., why are systemic antitumor immune responses only obtained from injection of tumor cells in the opposite flank? Are there any data that demonstrates immune cell activation in an *in vitro* system? Do the investigators possess adequate expertise to reproduce the number of viable tumor cells required for this study? The RAC should not approve this experiment based on the incomplete nature of the preclinical data, the unsatisfactory Informed Consent document, and the high risk/benefit ratio to these patients.

Other Comments

Dr. Haselkorn asked the investigators to summarize the information that was gained from the patient that was approved to receive gene transfer on a compassionate plea basis. Ms. Meyers suggested the inclusion of a statement in the Informed Consent document regarding patient confidentiality. Dr. Leventhal inquired about the process for obtaining tumor specimens from patients whose primary tumor has already metastasized.

Investigator Response--Dr. Sobol

Dr. Sobol agreed to incorporate Ms. Meyers' suggestion about patient confidentiality into the Informed Consent document. In response to Dr. Leventhal's question about access to tumor specimens, Dr. Sobol stated that tumor cells will be obtained at the time of colon resection, even if the patient has metastatic disease. Those tumor specimens will be cryopreserved. Dr. Leventhal said that the Informed Consent document should be revised to include a statement that clearly explains that patients will have their primary tumors cryopreserved at the time of resection. Responding to questions about the *in vivo* data, Dr. Sobol said that 3 separate animal studies were performed. One experiment demonstrated an antitumor response effected by IL-2 transduced fibroblasts and noted that this response was not T cell-mediated. The second experiment demonstrated an antitumor response associated with a low level of IL-2 production; whereas, no antitumor response was observed at high levels of IL-2 production. A third experiment was conducted in which animals were first challenged with a live tumor transplant. Dr. Parkman explained that the animal studies are inconclusive regarding the optimum concentration of IL-2 for the proposed human study. Dr. Chase stated that although the protocol does not present any significant risk, there is no significant scientific conclusion derived from the preclinical studies that can be translated to the human study. Dr. Parkman noted that the investigators propose to treat colon cancer with the IL-2-producing cells, an aspect different from other previously approved protocols. Dr. Post added that animal experiments often are of limited value for human studies; therefore, the positive antitumor responses obtained from these studies should be considered.

Dr. Sobol explained that if no toxicity is observed, 9 patients will be treated (3 patients in each of the 3 dose groups). If toxicity is observed, a larger number of patients will be required to define a safe dose. Dr. Straus suggested that accrual should be limited to a maximum of 12 patients. Dr. Sobol agreed to accept this upper limit of patient accrual. Dr. Sobol stated that a volume of between 100 and 200 milliliters (ml) of blood will be drawn at each immunization (i.e., a total of 400 to 800 ml over a two month period). Dr. Straus remarked that this volume of blood is higher than the allowable research limit. Dr. Sobol agreed to use the lower volume, 100 ml, of blood to be drawn at each immunization. Dr. Sobol agreed to revise the Informed Consent document and nontechnical abstract as suggested by the RAC. Regarding the lethal irradiation of cells, Dr. Sobol said that additional experiments are ongoing to determine the lethal dose of radiation.

Committee Motion

A motion was made by Dr. Parkman and seconded by Dr. Post to approve the protocol. RAC approval of the protocol is contingent on the review and approval of the following by the primary reviewers: (1) a revised Informed Consent document (incorporating the changes suggested by RAC members), (2) patient accrual will be limited to 12 patients, (3) data demonstrating lethal irradiation of tumor cells and fibroblasts, and (4) a revised patient eligibility criterion that limits the study to those patients who undergo treatment for their primary tumor (i.e., available tumor cryopreserved) at Sharp Memorial Hospital, San Diego, California. The motion to approve the

protocol passed by a vote of 14 in favor, 0 opposed, and 2 abstentions.

X. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED* : *INJECTION OF GLIOBLASTOMA PATIENTS WITH TUMOR CELLS GENETICALLY MODIFIED TO SECRETE INTERLEUKIN-2 (IL-2): A PHASE I STUDY/DRS. SOBOL AND ROYSTON*

Review--Dr. Krogstad

Dr. Walters called on Dr. Krogstad to present his primary review of the protocol submitted by Drs. Robert E. Sobol and Ivor Royston of the San Diego Regional Cancer Center, San Diego, California. Dr. Krogstad said that this Phase I study involves glioblastoma patients. The objectives of this study are to: (1) to evaluate the safety of subcutaneous immunization with irradiated autologous or allogeneic HLA-A2 (human leukocyte antigen-A2) positive glioblastoma cells modified to secret IL-2, (2) evaluate the efficacy of these immunizations on tumor growth, (3) induce cellular or humoral responses by this process, and (4) compare responses induced by autologous versus allogeneic tumor cells. The rationale for this study is based on published data demonstrating that the HLA-A2 locus is a dominant haplotype for tumor antigen presentation. The investigators propose that peripheral immunization with IL-2 transduced allogeneic glioblastoma cells will induce immune responses that will cross the blood-brain barrier from the systemic circulation into the brain. The investigators cite a study by Mahaley, et. al., that suggests the prolonged survival of patients following such immunizations. However, this study is difficult to interpret because these patients underwent other forms of treatment simultaneously.

Dr. Krogstad explained that the investigators propose to use the retrovirus vector, G1NaCvl2.2 (Genetic Therapy, Inc), with a human IL-2 cDNA insert. This construct has been previousl approved by the RAC for other human gene transfer studies. He expressed concern that allocating patients to 2 arms of the study may complicate interpretation of the data. He questioned whether the state of the art technologies (e.g., MRI and CT (computerized tomography)) wil accurately assess questions of treatment, toxicity, and efficacy. Since the basis for this proposed study is data derived from a single patient study, issues such as toxicity and efficacy may not be accurately addressed. However, useful information may be gained about the immunologic effects of the proposed experiment.

Review--Dr. Chase

Dr. Chase agreed that useful information may be obtained from the immunological studies; however, this proposal is based on dubious neuroradiology of a single patient who received otl forms of treatment (e.g., chemotherapy and radiotherapy) immediately prior to and during the course of the gene transfer study. Neither scientific or medical information may be obtained from treating additional patients on a protocol that is based on non-definitive data. He recommended disapproval of this protocol.

Review--Ms. Meyers

Ms. Meyers said that many of her initial concerns about the Informed Consent document have been addressed by the investigators. However, there are several remaining issues that should be addressed by the PI. Why are the investigators proposing to use cryopreserved , allogeneic c obtained from the deceased patient? She cited the California court decision (John Moore versus the University of California) in which the court ruled that any commercial preparation derived from

a patient's cells is the property of that patient, and the manufacturer must obtain permission for the use of such cells and provide compensation. Has written permission been obtained for the use of these cells prior to the patient's death? Although a minimum expected survival (3 months) has been defined, a maximum expected survival (i.e., 1 year) should be included. The Informed Consent document should be revised to include a statement about patient confidentiality and protection from the media. She expressed her displeasure about the inaccurate press report by Reuters Information Services, Inc., which suggests that the single patient trial was efficacious.

Other Comments

As a follow-up to Ms. Meyers comments and regarding the inaccuracy of the Reuters press report about the single patient trial, Dr. Haselkorn asked the investigators about two quotations: (1) "t patient lived several months longer than the average life expectancy of a person suffering with the particular form of incurable brain cancer," and (2) "the fact that we were able to demonstrate an immune response against the tumor suggests additional evaluation of patients is warranted." Dr. Leventhal expressed her objection to the statements made in the Reuters news report. The pati treated on the single patient trial received Decadron , Tamoxifen , and other forms of antit therapy. It is impossible to draw any scientific conclusions about the effects of the gene transfer. Dr. Leventhal disagreed with the investigators' interpretation of the immunological data obtaine from the single patient. The preliminary data does not support approval of this proposal.

Dr. Walters called on Dr. Parkman to interpret the immunological data obtained from the previous patient. Dr. Parkman stated that the investigators used an*in vitro* system to evaluate the cytolytic capacity of peripheral blood lymphocytes. The data derived from these*in vitro* experiments demonstrates a slight increase in cytolytic activity in response to this treatmen

Investigator Response--Dr. Sobo

In response to Ms. Meyers' concern that an autopsy was not obtained on the single patient who died while on the previous trial, Dr. Sobol explained that the family denied the request for autop However, *in vitro* experiments were performed with cells obtained from this patient. Although the data suggest an increase in cytotoxic T lymphocyte (CTL) activity following tumor cell inject the responses were variable. The reasons for this variation are unclear. Dr. Smith inquired about the numbers of times that patient's pretreatment level was measured. Dr. Sobol responded tha this assay had been performed twice. Drs. Smith and Chase suggested that the variation observed in the data may be a result of random variation and not a result of the treatment.

Dr. Sobol explained that the proposed study will provide definitive information about antitum activity because of the number of patients who will be accrued. Data derived from this larger study will yield statistically significant results. The proposed study will provide useful information about autologous versus allogenic immunization. Allogeneic stimulation would provide a less c approach to this treatment.

In response to Dr. Parkman's question about the allogeneic cell line, Dr. Sobol explained tha tumor cell line was established from the patient treated on the previous trial. This allogeneic ce line will be transduced with a different retrovirus vector than was used for the previous trial. Th new vector will produce higher levels of IL-2.

With regard to the*in vitro* data, Dr. Straus asked if the variation in CTL activity and the clinica responses observed could be a result of the other concurrent therapies (e.g., steroids) the patient

was receiving. Dr. Sobol answered that although the patient received prolonged Decadr treatment, the antitumor activity and clinical changes could be a result of high IL-2 expression l the transduction of cells. Dr. Straus disagreed with the investigator's interpretation of these results. Dr. Miller stated that these preliminary data are insufficient to support the proposal because the results are not interpretable.

Dr. Carmen stated that the NIH Director should never have permitted this single patient protoco be performed. No scientifically valid data can be derived from this single patient protocol. The investigators failed to provide evidence of preclinical efficacy in an appropriate animal model.

Committee Motion

A motion was made by Dr. Carmen and seconded by Dr. Brinckerhoff to disapprove the protoco Dr. Post remarked that a relevant animal model is not available for human brain cancer. Dr. Sobo said some *in vivo* experiments had been performed in which rats were immunized with glial tum cells modified to produce IL-2; however, no antitumor effects were observed. Dr. Straus noted t the investigators have made a great effort to propose an experiment designed to treat a very desperate disease; however, the protocol lacks sufficient preclinical data to provide a scientific basis for the study. For these desperate patients, many therapies are given to patients that complicate the study. If these alternative treatments are withheld from patients because of some false promise of gene therapy, the investigators could harm the patients. Lacking other supportive studies, Dr. Straus recommended disapproval of this study.

Dr. Parkman explained that he would not vote for disapproving this protocol. The RAC has approved other protocols with similar preclinical data. Since the investigators propose to use lethally irradiated cells, there is minimal risk associated with the experiment. The potential risk to patients is that other forms of therapy may be withheld from these patients.

Dr. Haselkorn stated that there are other forms of harm that could occur as a result of a patient' participation in this study such as psychological harm to the patient's family based on false expectations and discrediting the reputation of the medical research community because of misrepresentation of data (i.e., the Reuters new report). Dr. Sobol responded that he does not h control over the press. Dr. Leventhal quoted a statement from a scientific abstract that wa submitted by the investigators to the International Conference on Brain Tumor Research and Therapy 1993: "these encouraging results suggest that evaluation of this form of IL-2 gene therapy in additional patients with glioblastoma is warranted." Dr. Smith stated that immunolog data obtained from the single patient trial are uninterpretable ; however, the animal data provide support of the investigators' colon cancer protocol should be considered acceptable preclinical data for the glioblastoma study. Immunological experiments could be redesigned to assess th baseline that would render the present data interpretable. Additional immunophenotype data ar necessary.

Dr. DeLeon stated that the RAC should be objective and consistent in its review and approval o protocols. Since the investigators have provided *in vitro* data as well as *in vivo* data to support the colon carcinoma protocol, she recommends approval of this protocol. Dr. Krogstad said that th protocol could be strengthened to obtain interpretable data. Dr. Krogstad said that the RA should consider approval of this study on the basis of the material submitted, and should not consider the confrontational circumstances in which the single patient protocol was approved.

The motion to disapprove the protocol passed by a vote of 10 in favor, 5 opposed and 1

abstention. The majority of the RAC members concluded that the preclinical data derived from a single patient protocol was inadequate to justify the proposal.

XI. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GEN TRANSFER PROTOCOL ENTITLED: RETROVIRUS-MEDIATED TRANSFER OF THE cDNA FO HUMAN GLUCOCEREBROSIDASE INTO PERIPHERAL BLOOD REPOPULATING CELLS O PATIENTS WITH GAUCHER'S DISEASE/DR. SCHUEN*

Review--Dr. Haselkor

Dr. Walters called on Dr. Haselkorn to present his primary review of the protocol submitted by D Friedrich Schuening of the Fred Hutchinson Cancer Research Center, Seattle, Washington. Dr Haselkorn noted that the RAC has previously reviewed and approved other gene transfe protocols for the treatment of Gaucher's disease. Gaucher's disease is caused by a genetic in which the lack of glucocerebrosidase (GC) production results in the accumulation o glucocerebrosides . Current therapy consists of periodic injections of the purified human enzym This enzyme is found principally in small amounts in the placenta. The cost of treatment for a typical affected adult approaches $400,000 per year. Since enzyme replacement therapy has been demonstrated to alleviate symptoms in Gaucher patients, gene therapy is a logical next approa The investigators propose to collect autologous peripheral blood cells, isolate CD34(+) stem ce (which are capable of repopulating bone marrow), and transduce these cells with a retrovira vector containing the human GC gene. These transduced cells will then be reinfused into patient. Dr. Haselkorn asked the investigators to provide additional information about the level GC expression by transduced CD34(+) cells. How does the level of GC expression observed b the investigators compare to the levels of expression observed by Drs. Barranger (University o Pittsburgh) and Karlsson (NIH)? Have experiments been performed comparing the propo vector with the other two RAC-approved GC vectors? Commercial considerations should be ignored so that the optimum vector is proposed for all trials. Dr. Haselkorn expressed concer about the RAC's recommendation for approval of 3 simultaneous trials for the same disease Preferably, the RAC should wait to obtain results from the ongoing studies before approving additional trials. Dr. Haselkorn noted that Dr. Schuening has not accrued any patients onto e of his previously approved trials for breast cancer and lymphoid malignancies.

Review--Dr. Brinckerhof

Dr. Brinckerhoff stated that the current forms of therapy for Gaucher's disease, enz replacement and bone marrow transplantation, have shortcomings. Therefore, there is significant rationale for proposing gene therapy as a treatment for this disease. Although the investigators have conducted several preliminary *in vivo* and *in vitro* experiments, the data are diffuse and inconclusive. Dr. Brinckerhoff asked about the level of gene expression necessary to demonstr efficacy in the humans. Although the investigators have demonstrated GC gene expression in fibroblasts, it is unclear how this data extrapolates to humans. Preliminary data does not demonstrate the duration and level of GC expression. Although long-term expression of the neomycin resistance (neoR) gene was demonstrated using the proposed vector, the investigato were unable to co-transfect the ADA gene. Data has not been provided demonstrating long-term GC expression. Although the murine data were encouraging, the canine experiments wer inadequate. Quality assurance data on the modified retrovirus vector, LgGC , and the packagin cells are inadequate. Is a 15 to 20% correction of the GC enzyme activity in these patients sufficien to alleviate the clinical symptoms? Will the investigators be able to achieve the proposed level of gene expression? Dr. Brinckerhoff recommended deferral of this protocol until the RAC has ha

the opportunity to review additional expression data.

Review--Dr. Carmen

Dr. Carmen stated that the only novel feature about this study over the previously approved Gaucher's disease protocols is that a new retrovirus vector, LgGC , is being proposed. LgG been safety modified to reduce the risk of RCR . The investigators propose to use a new packag cell line, PG13, to enhance gene expression. Preclinical safety testing data has not been submitted for this LgGC /PG13 system; however, the investigators note that similar data was not required f approval of Dr. Barranger's protocol of Gaucher's disease. Dr. Carmen recommended that RAC maintain consistency in its review and approval of similar protocols. If accelerated review is adopted by the RAC, this protocol is an example of experiments that may qualify. In this particular situation, the onus would be on the investigator to provide satisfactory preclinical safety testing data for the new vector. He submitted several recommendations to the Informed Consent document to make the document more understandable to laypersons.

Other Comments

Dr. Parkman noted his intention to abstain from voting on this protocol due to conflict of interest (participated in a similar protocol at the University of Southern California). He commented that there may be a benefit to having 3 simultaneous trials for the same disease but utilizing 3 slightly different vector constructs. Biologically relevant information would be obtained in a shorter time frame. He expressed concern about whether data is conclusive about GC expression in hematopoietic stem cells, despite demonstration of such expression in other cell types such a fibroblasts. Dr. Haselkorn expressed concern about Dr. Schuening's inability to obtain adeq levels of GC expression using one of the other vectors previously approved by the RAC. Dr. Haselkorn noted that it was important for the PIs of these similar trials to maintain communicat with other investigators about scientifically relevant data. Ms. Grossman stated that perhaps the investigators' failure to reproduce previous experiments is due to lack of experience with particular techniques. Dr. Parkman explained that expertise is a key element that must be considered especially when the RAC begins to consider multi-center trials. Investigators must demonstrate successful transduction even when the same vector and target cells are proposed.

Dr. Post asked the investigators to provide additional information about RCR testing of th LgGC /PG13 system. A ne *en*gene has been introduced into this system.

Investigator Responses--Dr. Schuenin

In response to the RAC's concerns about the choice of vector, Dr. Schuening said that he collaborated extensively with Dr. Barranger on these preclinical studies. In regard to the issue o the optimal vector for stem cell transduction, the human clinical trials will most adequately addres this question. Both the MFG-GC vector (used by Dr. Barranger) and the LgGC vector yield si results with regard to *in vitro* transduction of human progenitor cells. Dr. Schuening clarified a earlier statement about the inability to reproduce similar levels of GC expression with Dr. Karlsson's vector. He was referring to the transduction experiment in which stromal mono were employed to maintain long-term repopulating cells. No patients have been accrued onto Dr. Karlsson's previously approved protocol because he is awaiting FDA approval. Dr. Leventh remarked that Dr. Schuening's semi-annual data report form included a statement that the reas for closure of the protocol on Hodgkin's disease was due to reported toxicities associated with IL-3. Dr. Schuening responded that a subsequent minor modification has been submitted in wh

permission is requested to replace IL-3 with the less toxic fusion protein, GM- CSF /IL-3, fo mobilization of CD34(+) cells in the peripheral blood from bone marrow. Review of this minor modification is in progress.

In response to Dr. Brinckerhoff's question about the preclinical studies, Dr. Schuening expla that he has performed numerous experiments (*in vitro* and *in vivo*) using the proposed vector. The experiments have included small animals, large animals, established cell lines, and normal human hematopoietic progenitor cells. Data demonstrates that the GC enzyme levels in normal cells ar increased above endogenous levels. These levels of increase are even higher in fibroblasts obtained from Gaucher patients, e.g., 12- to 18-fold over nontransduced controls. With regar long-term animal data, canine experiments have demonstrated expression of *neo*R out to 4 years following transplantation of transduced marrow cells. The inability to detect the co- transfect ADA gene in these animals was due to the high level of endogenous ADA activity.

Responding to Dr. Carmen's question about preclinical canine safety data, Dr. Schuening said t two animals have received LgGC transduced marrow cells and have been observed approximately 6 months. No evidence of toxicity has been observed.

Dr. Miller stated that, as a collaborator on this protocol, he would respond to the RAC's questio about the retrovirus construct and packaging cell line. It is difficult to conduct comparison studies between investigators using different vector suppliers because of commercial considerations. Development and validation of vectors is extremely costly for the companies involved. The 3 GC vectors reviewed by the RAC are more similar than different. All of these vectors are all based on the Moloney murine leukemia virus (MoMuLV). The LgGC vector has a modified t-RNA that eliminates the problem associated with expression by protein binding. Preliminary data indicate that this modified binding site allows the vector to express the gene insert better in fibroblasts than other vectors; however, there is no definitive data about this benefit in bone marrow expression to date. However, *in vitro* transduction of human bone marrow cells with the LgGC vector demonstrates increased GC activity, which is an indicator of gene expressio

Dr. Tom Reynolds from Targeted Genetics Corporation, Seattle, Washington, explained the RCR testing procedures. The most likely mechanism for generating RCR is homologous recombinati between the vector and the retroviral genes inserted in the packaging cells. The LgGC vector la the retroviral *en*gene, and the PG13 packaging cells were made by independent introduction of the *gag- po*genes of MoMuLV and th*en*gene of gibbon ape leukemia virus (GALV) into th NIH3T3 TK - cells. These modifications were introduced to reduce the probability of generatin RCR by recombination between th*en*genes of the vector and the packaging cells. Targeted Genetics Corporation is developing improved assays to detect potential GALV recombinants. T human HeLa cell line, which is susceptible to GALV infection, will be used as a rescue cell li Upon infection of the HeLa cells with RCR , the rescued vector is detectable by its hygrom selectable marker. The sensitivity of this rescue assay is currently being determined. Dr. Miller explained that S+L - assays have been performed, and there is no evidence of RCR using the cell line. Dr. Post suggested that approval of this protocol might be contingent on the submission of RCR sensitivity assay

Ms. Meyers asked whether recommendations for long-term follow-up and contraception for men/women were included in the Informed Consent document. Dr. Schuening replied that thes issues have been addressed in the document. Dr. Parkman inquired about the length of time necessary for contraception to be practiced. If the experiment is successful, the inserted gene will persist during the life of these patients. Dr. Zallen said that it is reasonable to require contracep

during the active phase of the gene transfer protocol.

Committee Motion

A motion was made by Dr. Haselkorn and seconded by Dr. Carmen to approve the protoco contingent on the submission of data demonstrating the level of sensitivity of assays for RCR a review and approval of this data by the primary reviewers. The motion to approve the protocol passed by a vote of 13 in favor, 0 opposed, and 3 abstentions.

XII. DISCUSSION ON INFORMED CONSENT ISSUES/DR. ELLIS

Dr. Zallen , Chair of the RAC Working Group on Informed Consent, presented an overview of th written questions that were forwarded to Dr. Gary Ellis, Director of the Office for Protection from Research Risks (OPRR) of NIH , prior to this meeting. She thanked Dr. Ellis for his willingnes present an oral response to the working group's questions.

Dr. Zallen explained that the working group focused its concerns in three areas: (1) the role o OPRR and its mechanism for oversight of local IRBs , (2) the relationship between IRBs a (e.g., quality control for Informed Consent documents), and (3) the independent responsibilities and cooperative efforts of the RAC, OPRR , and IRBs , particularly in relation to human g transfer. The RAC frequently encounters resistance from local IRBs concerning recommende changes to Informed Consent documents. Dr. Zallen inquired whether the RAC, as part of it advisory role, can condition its approval of a given protocol contingent on Informed Consent document changes. Dr. Zallen asked Dr. Ellis for recommendations on how to resolve issues i which there is disagreement between the RAC and the local IRB

Dr. Ellis explained that OPRR is an office within the Department of Health and Human Services, housed at NIH . OPRR oversees implementation of the federal regulations for the protection human subjects and oversees approximately 1,000 IRBs in the United States. OPRR dischar responsibility through a process of assurance negotiation. For large institutions, multiple project assurances are franchised by OPRR . Each institution is responsible for the review of all Inform Consent documents and oversight of the consent process. For smaller institutions, the local IRB work in tandem with the OPRR through single project assurances. The only Informed Consen documents routinely reviewed by OPRR are those from small institution

Dr. Ellis said that a very important component of the oversight system is vesting the IRB with th authority for oversight of the Informed Consent process at the local level since the IRB is in th best position to reflect the local and state laws, institutional policies and responsibilities, and diversities in patient population. OPRR provides informal guidance through periodic contact wi the institution, informational conferences, and through the newsletter, *OPRR Repar*

OPRR assures compliance through a formal mechanism. The Federal regulations include eigh elements that must be considered when drafting an Informed Consent document. The RAC can forward recommendations (e.g., specific to gene transfer) to OPRR for inclusion in Informe Consent documents. If endorsed by OPRR , the recommendation would be transmitted to the lo IRBs throug *OPRR Repar*Dr. Ellis suggested the RAC could amend the *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects (Points to Consider)* to include pertinent issues that need to be addressed in the Informed Consent document and would work in tandem with the IRBs to educate investigator with regard to the preparation of Informed Consent documents for human gene transfer protocols.

Ms. Meyers asked who has the final authority over Informed Consent documents, the RAC or the IRB . Dr. Ellis explained that while the IRB has purview over these documents, the RAC is i position to recommend necessary changes. Dr. Zallen asked if the NIH Director has the auth to overrule the local IRB . Dr. Ellis said that the Director has ultimate authority over NIH resea grant awards. Since the NIH Director can withdraw grant monies, IRB's tend to comply with regulations and recommendations so their funds will not be jeopardized.

Dr. Parkman said that Dr. Ellis has suggested a very clear two-prong approach with regard to Informed Consent documents; therefore, the working group should now be charged with developing *suggested* language for recommendation to OPRR and th*Points to Consider* document.

A lengthy discussion ensued about compensation for costs associated with research-related injuries, an issue that frequently remains unresolved between the RAC and local IRBs . Dr. Elli agreed that there are serious ethical considerations if patients were required to pay for such costs; however, these issues are beyond the scope of OPRR . The issue of compensation fo research-related injury has previously been addressed by the RAC and has been brought to the attention of the Health Care Reform Task Force of the Clinton Administration.

In conclusion, most RAC members agreed with Dr. Ellis' suggestion that the RAC should draft a letter outlining the specific recommendations to the OPRR for consideration and distribution t local IRBs as well as proposed amendments to th*Points to Consider*. The working group should develop language that addresses the following: (1) recommendations for contraception by males/females, (2) responsibility for financial costs of the experiment, (3) the necessity for long-term follow-up, (4) request for autopsy, and (5) protection of patient confidentiality when information is released to the media.

XIII. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GEN TRANSFER PROTOCOL ENTITLED: AN OPEN LABEL, PHASE I/II CLINICAL TRIAL TO EVALUATE THE SAFETY AND BIOLOGICAL ACTIVITY OF HIV- IT(V) (HIV-1 IIBenv /RETROVI VECTOR) IN HIV-1 INFECTED SUBJECTS/DR. HAUBRIC*

Review--Dr. Straus

Dr. Walters called on Dr. Straus to present his primary review of the protocol submitted by Dr. Richard Haubrich of the University of California at San Diego Treatment Center, San Diego California. The primary objectives of this protocol are to evaluate safety and to ascertain the immunological effects of the human immunodeficiency virus (HIV)- IT(V) vector in HIV-1(+ asymptomatic individuals. The treatment is designed to stimulate a CTL response against th HIV-1 *env* /proteins. This response could lead to a reduction in the number or elimination of HIV-infected cells. Enhanced viral clearance could reverse immunosuppression or inhibit it progression. This proposal represents an extension of Dr. Galpin's previously approved protoc in which a murine retroviral vector containing HIV*tev* and *en*genes was injected intramuscularly into HIV(+) subjects. This current proposal incorporates the following modifications as compared to Dr. Galpin's protocol: (1) patient eligibility will be expanded t include patients with CD4 counts between 200 and 499, (2) the highest virus inoculum propose for this study is 107 cfu , (3) doses will be administered to multiple muscle sites, (4) doses will b administered at 3 monthly intervals rather than biweekly intervals, and (5) antiviral therapy will be permitted but withheld for 3 days prior to and 3 days following vector injection. The vector, study

rationale, and the preclinical data are well presented. The Informed Consent document is acceptable with the inclusion of modifications relating to request for autopsy and long-term follow-up. There are still several outstanding issues that should be addressed by the investigators. The current proposal is an extension of a previous study from which data is not yet available. The investigators should verify that the previous doses, including the 107 cfu propos for this study, have been well tolerated. The investigators should explain the rationale for proposing multiple injection sites, i.e., was a single injection site inadequate to confer a maximal response? Even though no interpretable data has been reported for the Phase I study, the investigators are requesting expansion to a Phase II trial. Although the vector may be safe, the RAC should carefully consider accelerated transition through these phases. The Informed Consent document contains an awkward and misleading statement about injuries arising in the course of the study will be covered except when they are "a consequence of research procedures designed directly to benefit..." the subject. Since this study may offer the potential of benefit, this statement could be interpreted that no coverage would be forthcoming. The investigator has provided a thorough response and a summary of the clinical experience with the 12 patients treated. No serious adverse effects were observed at any dose. In his written response, Dr. Haubrich states that this Phase I/II trial will not be initiated until the 12 subjects enrolled in th existing Phase I study have completed a full course of HIV- IT(V) or placebo injections. Prelimina data indicate that this treatment is safe; therefore, the protocol should be approved.

Review--Dr. Dronamraju (presented by Dr. Walter

Dr. Walters summarized Dr. Dronamraju's written review. Although the animal data justifies thi protocol, data has not been provided from the ongoing human study. The total number of patients accrued onto each stratum of the study should be clarified. The Informed Consent document acronyms should be revised so that terms such as CTL and HIV- IT(V) are clearly defined and comprehensible to laypersons. The Informed Consent document should include a request for autopsy. He inquired whether the "Experimental Subject's Bill of Rights" is a standard component of all protocols at the institution.

Review--Dr. Secundy (presented by Dr. Walter

Dr. Walters summarized Dr. Secundy's written comments. The data from the previous huma study is insufficient with regard to CTL activity, antibody response, viral burden, and possibl adverse effects. How long were the murine and baboon experiments carried out? Wha mechanisms are in place to ensure access to this study by women and minorities?

Other Comments

Dr. Carmen said that the Informed Consent document is unacceptable in its present form and submitted specific changes in writing that would make the document more comprehensible to laypersons. He inquired whether the patient information brochure prepared for Dr. Galpin's stu would be given to patients considering participation in this study. Dr. Parkman inquired about the length of time the vector sequences will persist at the injection sites.

Ms. Meyers stated that the Informed Consent document is very poorly written. Approval of this protocol should be contingent on review and approval of a revised Informed Consent document. Ms. Meyers agreed with Dr. Straus' interpretation of the compensation for research-related injury clause. This statement should be deleted from the Informed Consent document.

Discussion ensued about how the RAC could relay its concerns to Dr. Haubrich's IRB about Informed Consent statements concerning compensation for research-related injury. Dr. Krogstad suggested that the protocol should be deferred with the stipulation that university representatives and/or the IRB Chair be present at the RAC meeting when the protocol is resubmitted for review Dr. Parkman remarked that the present proposal is a Phase I/II trial that by definition is not for the benefit of the patient because there is no demonstration of efficacy. The sentence regarding benefits in the Informed Consent is not operative in this trial. Dr. Leventhal added that even Pha III studies are considered experimental and may not necessarily benefit the patient. Dr. Leventhal suggested that the RAC send a letter to Dr. Haubrich's IRB requesting that the statement ab research-related injury be deleted from the Informed Consent document.

Mr. G'dali Braverman of ACT-UP applauded the investigators for modifying the inclusion crit concerning lower CD4 counts thereby allowing more patients to be eligible for this study than the previously approved protocol. He commented on several other inclusion/exclusion criteria from a patient's point of view, such as cross participation in other studies, lowering the eligibility age from 18 to 13, accrual of women and minorities, use of antivirals , mentioning of other experime protocols to patients and other minor points. Mr. Braverman recommended approval of th protocol if the RAC members' comments and questions are adequately addressed.

Investigators' Responses--Drs. Merchant and Haubric

Dr. Bruce Merchant, Director of Clinical and Regulatory Affairs, Viagene , Inc., San Diego California, responded to the RAC's questions regarding the retrovirus vector. Murine d indicates that the vector sequences are detectable out to 56 days at the site of the injection. No sequences were detectable in the ovaries, lungs, lymph nodes, spleen, or liver of either primates or mice during this period. No vector sequences were present in primate sperm; however, data is not yet available about viral sequences at the site of injection in this group of animals. Any patients considering participation in the proposed study will receive the patient information brochure (same as for Dr. Galpin's study) several days in advance of the study coordinato interview. The Informed Consent document will be signed by the patient only after the brochure has been read and discussed with the coordinator. In regard to compensation for research-related injury, Viagene would be responsible for any expenses involved in the event of research-relate injury. This policy is clearly stated in the patient information brochure; however, the IRB reques that this statement be removed from the Informed Consent document. Dr. Merchant encouraged the RAC to send a recommendation about this issue to the IRB . He agreed to include the Inform Consent document changes suggested by the RAC and expressed his appreciation for Mr. Braverman's comments and suggestion

Discussion

There was a brief discussion regarding whether the letter to the IRB should be a contingency fo approval of the protocol. Dr. Straus said that a stronger message would be sent to the IRB if thi letter was a contingency. He said that the letter can be sent out from ORDA . Dr. Chas recommended that the RAC take stronger action concerning the issue of research injury compensation. Dr. Zallen remarked that the Informed Consent review should be part of th protocol approval process and agreed that a letter should be sent to the IRB as a contingency f approval.

Dr. Parkman remarked that if the present treatment has no benefit to the patients, the statement on compensation for treatment intended to benefit is not operative. Dr. Merchant agreed to include a

statement in the Informed Consent to indicate that the present treatment has no known or expected benefit to patients.

Committee Motion

A motion was made by Dr. Straus and seconded by Ms. Meyers to approve the protocol with the contingency that the primary reviewers review and approve the following: (1) a revised Informed Consent document which includes changes suggested by the RAC and includes the *Participant Information* brochure as an Appendix; (2) the Informed Consent document should be revised to include the statement, "This treatment has no known benefit, and there is no expectation that there will be any benefit to you," and (3) a letter should be sent to the IRB of the University o California at San Diego by ORDA requesting the following paragraph be deleted from the Inform Consent document:

"If I am injured as a result of participation in this research, the University of California will provide any medical care I need to treat those injuries - except when they are a consequence of research procedures designed to benefit me directly. The University will not provide any other form of compensation to me if I am injured."

The motion to approve the protocol passed by a vote of 15 in favor, 1 opposed, and 2 abstentions.

XIV. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GEN TRANSFER PROTOCOL ENTITLED: A PHASE I TRIAL OF B7-TRANSFECTED LETHALLY IRRADIATED ALLOGENEIC MELANOMA CELL LINES TO INDUCE CELL-MEDIATED IMMUNIT AGAINST TUMOR-ASSOCIATED ANTIGENS PRESENTED BY HLA-A2 OR HLA-A1 IN PATIENTS WITH STAGE IV MELANOMA/DR. SZNO*

Review--Dr. Parkman

Dr. Walters called on Dr. Parkman to present his primary review of the protocol submitted by Dr. Mario Sznol of the NIH , Frederick, Maryland. Dr. Parkman explained that the investigators pr to enhance the immunogenicity of tumor cells by introducing the B7 gene into tumor cells lacki this antigen. Two signals are required to induce CTL activity. One signal is initiated when th melanoma antigen binds to the T cell receptor. The second signal originates from the binding of the B7 antigen to the CD28 receptor of T cells. Melanoma cells are resistant to CTL killing becau these cells do not express this secondary B7 signal. The investigators propose to introduce the B7 gene into melanoma cell lines to enhance immunogenicity . Preclinical *in vivo* data indicates introduction of the B7 gene into non-immunogenic tumor cells enhances tumor cell immunogenicity and induces CTL activity, which results in rejection of both B7-modified non-modified tumor cells. As compared to cytokine gene transfer protocols, this protocol has no possibility of adverse effects associated with systemic cytokine toxicity. As a point of clarification Dr. Parkman explained that the B7 antigen proposed for this study is different from the HLA-B7 antigen previously approved by the RAC for Dr. Gary Nabel's protocol (University of Michiga #9306-045). B7 is not an HLA antigen, but belongs to a group of accessory molecules that bind the CD28 receptor.

Dr. Parkman explained that the patient population will be limited to either HLA-A1 or HLA-A2 individuals to ensure the appropriate HLA match with the corresponding melanoma cell lines Approximately 50 patients will be divided into 3 dose escalation groups to assess toxicity. Each group will receive 6 injections of 107, 108, or 109 cells that have been lethally irradiated at 20,000

rads . The cDNA of the B7 gene will be expressed in the bovine papilloma virus (BPV) BCMGNeo-B7. The B7 gene is regulated by a CMV promoter and the neoR gene by the S promoter. No other gene products will be expressed from this construct. This vector will be transfected into 3 melanoma cell lines using DNA- liposomes (lipofection). Only plasmid D be used for the lipofection procedure; therefore, there is little risk of transmission of th transduced gene to host cells. High dose irradiation will render the tumor cells nonviable. Patie will be evaluated for immunological responses and evaluated for any toxicity associated with the transduced tumor cell

Dr. Parkman inquired whether the HLA-A2 patients will receive injections of all 3 transduced melanoma cell lines on a rotating basis, and the HLA-A1 patients will receive only the HLA-A1/HLA-A2 cell line. Since 40% of Caucasians are HLA-A2, perhaps the protocol should be limited to this population in order to simplify interpretation of the data. He inquired about the necessity to accrue 50 patients on the proposed study. If a total of 6 patients are proposed for each dose group, 18 patients should be accrued. What is the rationale for injection of untransduced cells? Is there additional data demonstrati*in vitro* CTL responses? Since th scientific end point of this study is production of a CTL respons*in vitro* preclinical CTL dat must be provided. The PI has submitted additional data in response to the written primary review; however, there are several remaining questions regarding specificity of cell killing and the HLA type or subtype of the normal donor cells.

Review--Ms. Grossman

Ms. Grossman noted that many of her concerns were addressed by Dr. Parkman. The preclinical data demonstrating *in vitro* CTL activity are inadequate, the vector sequence is inadequate, an there are no preclinical animal studies. She expressed concern that ectopic B7 expression migl lead to the development of autoimmune disease due to immunogenicity to nontumor antige Based on the lack of scientific and immunologic data, this protocol is thought to be premature and not be recommended for approval.

Dr. Parkman stated that scientific rationale for injection of untransduced cells was not wel presented. This part of the protocol should be separated from the gene transfer protocol. Since the specificity of the CTL response has not been demonstrated, approval of the protocol is no justified.

Review--Dr. Zalle

Dr. Zallen questioned the scientific basis for treating HLA-A2 patients with a rotation of 3 differe cell lines. She expressed concern about the Informed Consent process. Approximately 38% of the subjects recruited onto this study will later be informed that they are ineligible to participate based on the results of the HLA typing. How will the investigators deal with the emotiona disappointment expected in these individuals? The protocol includes the statement "the financial costs of treatment are borne by the Biological Response Modifiers Program (BRMP) of th National Cancer Institute". However, this statement is not included in the Informed Consent document. The Informed Consent document should be revised to include requests for autopsy and long-term follow-up.

Other Comments

Dr. Geiduschek asked about the dilution of vector sequences following cell expansion. Since th

BPV vector is non-replicating, will the vector be present after expansion of the transfected *in vitro*? Is the level of B7 expression stable in the clonal cell line

Dr. Leventhal agreed with Dr. Zallen's concern that the Informed Consent document does properly inform subjects that they may be ineligible to participate in the study if determined not to be HLA-A2 or HLA-A1. Dr. Leventhal said that the Informed Consent document is too assertive for a Phase I experimental study and is unclear about how patients will be assigned into the control and experimental groups.

Dr. Carmen asked about Ms. Grossman's question about the incomplete vector sequence. A discussion ensued about the necessity to submit a complete sequence of every vector submitted for RAC review. Dr. Miller said that an assembled sequence is adequate for the current proposal. The investigators have demonstrated the functionality of the gene insert, the most important test for this construct. Since this gene construct is not proposed for a therapeutic purpose of correcting a gene deficiency, determination of the entire sequence of the gene insert is not essential. Insisting that the entire construct be sequenced would incur additional costs that are unnecessary. Dr. French Anderson of the University of Southern California noted that the *Points to Consider* require investigators to provide either a complete nucleotide sequence analysis or a detailed restriction enzyme map of the construct. There is no absolute requirement to totally sequence every gene construct.

Investigator's Responses--Drs. Fenton and Szno

Dr. Robert Fenton of the National Cancer Institute, NIH , Bethesda, Maryland, explained that substantial amount of information has been published in recent years regarding stimulation of immune responses by the B7 antigen. Dr. Fenton said that these published murine studies are the preclinical basis for the present human proposal. Although *in vitro* data demonstrating CTL activity was not submitted to the RAC, it was noted that these data are probably not critical for RAC review. With regard to B7 expression in transfected cell lines, only the highest B7-expressing clones were chosen. The vector sequences of these cloned cells were integrated into chromosomes at a rate of approximately one to two copies per cell. B7 expression is stable in these cell lines out to 14 days following lethal irradiation. Regarding the *in vitro* CTL activity preliminary data indicates melanoma-specific CTL activity. Peripheral blood cells obtained from HLA-A2 melanoma patients were mixed with a rotating panel of 3 transfected cell lines for 6 weeks Specific CTL activity was demonstrated toward melanoma cells. All donor cells have been typed for HLA

Dr. Fenton explained that the 3 transfected melanoma cell lines will be rotated to minimize the risk that patients will not be exposed to an important antigen and to specifically boost the A2 response. HLA-A1 patients will be included in this study to broaden patient eligibility. Patients will receive untransduced cells in order to serve as a control group for assessing the differences in expression. The BPV vector proposed for this protocol is similar to the vector previousl approved by the RAC for Dr. Podack's human gene transfer protocol, except that the early region of BPV has been deleted, which contains the transforming genes of this virus. As a consequence the present vector should be safer than the previously approved BPV vector. This deletio renders the vector incompetent for episomal replication. The gene is expressed only when the vector is integrated and into the target cell chromosome. Most of the vector sequences, with the exception of approximately 20 bases at the junction points, are included in the assembled sequence. The B7 gene is functional and the likelihood that the construct presents any significant risk to patients is small.

Dr. Sznol explained that all costs associated with patient participation will be covered by hi institution and agreed to work with his IRB to alter the statement about costs in the Informe Consent document. A request for autopsy was not included in the Informed Consent document because most patients who are accrued on this protocol will not die while participating in the experiment. However, if such a statement is required by the RAC, he will include the revision in the Informed Consent document. Dr. Straus commented that although an autopsy is often difficult to obtain, an autopsy is preferred due to the special concerns that are unique to gene therapy. It is important to demonstrate that the gene sequences did not persist in any tissues. Ms. Meyers said that several standard items are missing from the Informed Consent document, e.g., request for autopsy, request for long-term follow-up, and recommendations for male/female contraception. Dr. Leventhal remarked that most patients will probably die at a distant location; therefore, autops requests should be relayed to local physicians. Dr. Sznol agreed to incorporate the RAC suggested changes into a revised Informed Consent document.

Committee Motion #1

A motion was made by Ms. Grossman and seconded by Ms. Meyers to defer approval of the protocol on the basis of inadequate preclinical data.

Dr. Miller agreed with the investigators' assessment, that published studies adequately address the preclinical issues. Additional animal experiments will not add any new scientific information. Dr. Parkman said that his principal concern is that the end point of this study is to explicitly demonstrate melanoma-specific CTL responses; the data inadequately assesses th investigators' competence in performing these assays. Although the investigator's noted the existence of such data during their oral responses to the RAC, the data has not been submitted. Therefore, approval of the protocol should be deferred. Dr. Post said that published studies demonstrate the effect of B7 on tumor immunogenicity and provide strong justification for th present human study. Dr. Miller agreed with Dr. Post's assessment. Dr. Chase stated that he is inclined to defer this protocol. Dr. Geiduschek said that he is in favor of approving this protoco the basis that the preclinical data in question is not critical to support this proposal. Drs. Haselkorn and Leventhal stated their concern that the RAC is employing a higher standard f protocol than for previously approved studies; therefore, the protocol should be approved. Dr. Leventhal reminded the RAC that this protocol is a Phase I toxicity study; therefore, efficacy is a primary objective. Dr. Straus said that the scientific background for this human trial is compellin and recommends approval.

The motion to defer the protocol did not pass by a vote of 5 in favor, 12 opposed, and 1 abstention

Committee Motion #2

A motion was made by Dr. Post and seconded by Dr. Secundy to approve the protocol. Approva of the protocol is contingent on submission of the following: (1) data obtained from ongoing *in vitro* human melanoma experiments (to be reviewed by Dr. Parkman, but approval not required), and (2) inclusion in the Informed Consent document of a request for autopsy, a description of long-term follow-up, and a statement explaining that the study is non-beneficial (review and approval to be done by Drs. Leventhal and Zallen). A friendly amendment was made by Parkman and accepted by Drs. Post and Secundy to require that the Informed Consent docume be separated into a document for subjects receiving transduced cells and another document fo subjects receiving untransduced cells. The motion to approve the protocol passed by a vote of

in favor, 2 opposed, and 1 abstention.

XV. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GEN TRANSFER PROTOCOL ENTITLED: PHASE I STUDY OF IMMUNOTHERAPY OF ADVANCED COLORECTAL CARCINOMA BY DIRECT GENE TRANSFER INTO HEPATIC METASTASES/DR. RUBIN*

Review--Dr. Do

Dr. Walters called on Dr. Doi to present his primary review of the protocol submitted by Dr. Jos Rubin of the Mayo Clinic, Rochester, Minnesota. Dr. Doi stated that the primary objective of thi study is to determine the safety and feasibility of the direct injection of DNA/lipid complexes into hepatic metastases of patients with advanced colorectal carcinoma. This protocol is similar to Dr. Nabel's protocol that was previously approved by the RAC at its June 1993 meeting. There is n increased risk to patients in the present protocol, and the present approach is even more conservative than that of Nabel's . The investigators will attempt to stimulate *in vivo* immune response by direct intratumoral injection of lipid complexes containing genes encoding th HLA-B7 histocompatibility antigen and -2 microglobulin *In vivo* data demonstrates the attenuation of tumor growth; and in some instances, complete tumor regression as a result of this treatment. The DNA of the plasmid vector, pHLA-B7/-2, will be mixed with the cationic lipid, DMRIE (1,2-dimyristyloxypropyl-3-dimethylhydroxyethyl ammonium bromide), and the neutral lipid, DOPE (dioleoylphosphatidylethanolamine). These DNA/lipid complexes will be injected into the tumor a thin needle guided by sonography . The procedure has an accuracy rate of 98%. The injectio sites will be visualized and documented on videotape. Approximately 1% of cells within the tumor mass will be transfected . A total of 15 HLA-B7(-) colorectal patients with hepatic metastases wil treated in dose-escalation groups to determine toxicity. Patients will be divided into two treatment schedules. Toxicity symptoms such as fatigue, weight loss, nausea, vomiting, hemorrhage, infection, and liver chemistries will be evaluated during the test period and immunologic responses will be monitored. Most of the safety issues have been addressed. Although there is no control group in the present study and no clear description about the immune responses that will be monitored, Dr. Doi recommended approval of the protoco

Review--Dr. DeLeo

Dr. DeLeon said that this protocol is a conservative revision of Dr. Nabel's previously appro protocol. She noted some inconsistency in the number of hepatic injections between the Informed Consent document and the protocol. However, the investigators have clarified this issue. A request for autopsy should be included in the Informed Consent document. Dr. DeLeon recommended approval of the protocol.

Review-- Mr . Capron (presented by Dr. DeLe

Dr. DeLeon provided an overview of Mr. Capron's written review to the Informed Consen document. The term "therapy" should not be used because the investigational nature of the study is not adequately conveyed. Suggested language was submitted that would improve comprehension by laypersons.

Other Comments

Dr. Leventhal asked the investigators to compare the doses of DNA to those administered in Dr

Nabel's protocol. Ms. Meyers raised several concerns about the Informed Consent document, i. long-term follow-up, recommendations for contraception, and request for autopsy. Ms. Meyers asked the investigators to clarify the patient's responsibility for any costs related to the treatment.

Investigator Response--Dr. Kovach

Dr. John Kovach of the Mayo Clinic, Rochester, Minnesota, said that the major end point of this study is any observed change in the titer of anti-B7 CTL activity in the peripheral blood. Althou the investigators have to resolve certain technical difficulties involving assays of biopsy materials specific cytotoxicity of the untransduced tumor cells will be determined. With regard to Informed Consent document issues, all patients will have life long follow-up, and none of the costs of the research will be charged to patients. Changes will be made to the Informed Consent document to clarify these points. The current statement about research-related injury is derived from other protocols previously reviewed by the RAC. A request for autopsy will be included in a revised document.

Dr. Alan Schreiber of Vical , Inc., San Diego, California, clarified the discrepancy of the current D doses to that of the Nabel protocol. Dr. Schreiber noted Vical's intention to initiate this proto other sites and encouraged the RAC to adopt an accelerated review mechanism for similar trials. Dr. Parkman said that multi-institution studies can be encompassed by the current review mechanism if such information is available at the time of submission for RAC review.

Committee Motion

A motion was made by Dr. DeLeon and seconded by Dr. Doi to approve the protocol with stipulation that a revised Informed Consent document, including the changes suggested by the RAC, be reviewed and approved by the primary reviewers. The motion to approve the protocol passed by a vote of 18 in favor, 0 opposed, and no abstentions.

XVI. UPDATE ON DR. ROTH'S PROTOCOL ENTITLED: *CLINICAL PROTOCOL FOR MODIFICATION OF ONCOGENE AND TUMOR SUPPRESSOR GENE EXPRESSION IN NON-SMA CELL LUNG CANCER, #9209-031/DR. ROTH*

Dr. Walters called on Dr. Miller to present an update on the protocol submitted by Dr. Jack Roth of MD Anderson Cancer Center, Houston, Texas, that was approved with contingencies at the September 1992 RAC meeting. Dr. Miller summarized the chronology of events that have transpired since September 1992. RAC approval of Dr. Roth's protocol was contingent on: (1) submission of data demonstrating the transforming potential of 100 ml of retroviral supernatant analogous to the preparation that will be used for the clinical protocol, (2) submission of data obtained from *in vitro* mixing experiments, (3) submission of*in vitro* data demonstrating that the new vector preparations have activity, and (4) incorporation of minor changes in the Informed Consent document as noted by Drs. Carmen and Hirano.

On May 11, 1993, Dr. Roth submitted data in response to the stipulations and requested a minor modification to change the site of production of the clinical grade retroviral preparations from Genetic Therapy, Inc., to Microbiological Associates, Inc. After reviewing the submitted data, all three primary reviewers, Drs. Miller, Hirano, and Geiduschek , recommended disapproval. O September 22, 1993, and October 7, 1993, Dr. Roth submitted additional data. The three primary RAC reviewers subsequently recommended disapproval of this additional data submitted in response to the stipulation requirements, although the minor modification was approved. On

November 11, 1993, Dr. Roth submitted additional data and made a request for a compassionate plea exemption. The request for compassionate plea exemption was denied by ORDA o November 16, 1993, based on the "Procedures to be Followed for Expedited Review" (58 FR 2174). Drs. Miller, Geiduschek , and Hirano did not accept the additional data as fulfilling the stipulatio requirement. Dr. Miller suggested that the full RAC should discuss whether Dr. Roth's data adequately meets the stipulation requirements for approval. Upon request by Dr. Walters (Chair), Dr. Roth provided a written statement on December 1, 1993, providing his rationale that the stipulation requirements were adequately addressed.

Dr. Miller explained that there are concerns regarding safety and efficacy issues since this gene transfer protocol introduces oncogenes (which promote cancer development) and tumo suppressor genes (which retard tumor growth). The first stipulation was to provide data demonstrating lack of generation of transforming virus in 100 ml of the clinical grade retrovirus supernatants. Subsequent discussion between the primary reviewers and the investigator resulted in a modification of this stipulation. The revised stipulation is: "assay a single patient dose for the presence of transforming virus, i.e., 10 ml of supernatant at a vector titer of 1 x 107 cfu /ml (total of 108 cfu)." The data provided by the investigator in response to this stipulatio found to be inadequate due to lack of proper control experiments and the low level of sensitivity of the assay. The second stipulation involves the provision of data documenting the "bystander effect" claimed by the investigators, i.e., the ability of gene-modified tumor cells to suppress the growth of unmodified tumor cells. This "bystander effect" is crucial for efficacy of the present approach to suppress tumor growth, since only a small faction of tumor cells will be transduced by the vectors. Although there was an initial misunderstanding by the investigators with regard to this stipulation, Dr. Miller stated that he held extensive telephone conversations with Dr. Roth, in which the stipulation was explained and the investigator stated that he understood the necessary requirements. Dr. Miller noted that his comments with regard to this stipulation were outlined extensively in his review of this protocol. Data has never been submitted in response to this second stipulation. The third stipulation involves demonstration that there are no rearrangements in the vector structure during vector production from the producer cells. Dr. Miller stated that the new vector LNp53B, employs a *bidirectional* SV40 polyadenylation site that promote rearrangement and may result in vectors with unknown activity. Northern and Southern blot analyses of the vector structure, and transcription in producer cells would demonstrate that there is no such rearrangement. The investigators have not provided satisfactory data in response to this third stipulation. The fourth stipulation involves minor changes in the Informed Consent document. An amended document was submitted by the investigators and adequately meets this stipulation.

Dr. Secundy inquired about the length of time required to perform the necessary experiments. D Miller explained that the requested assays are relatively simple, taking only a few hours to set up, with several weeks of observation before the results are obtained. Time and cost are several reasons cited by Dr. Roth for not performing these experiments. Dr. Miller said that the investigato has stated that the protocol is justified on the basis that the proposed patient population is terminally ill. Dr. Chase said that this latter rationale is invalid. Dr. Walters stated that the consensus of the committee should be obtained with regard to recommendations for this protocol.

Dr. Post suggested that because of the lengthy delays that have occurred, the protocol should be resubmitted for reconsideration by the full RAC. Drs. DeLeon , Krogstad , and Ms. Gross supported this suggestion. Dr. Geiduschek stated that a protocol cannot be considered approv by the RAC unless all stipulation requirements have been met. Dr. Leventhal suggested that th

protocol should be resubmitted, and that different primary reviewers should be assigned. Dr. Parkman said that approval of this protocol should be considered administratively inactivated due to failure to meet the stipulation requirements.

Committee Consensus

The consensus of the RAC was that Dr. Roth should resubmit a revised protocol, including all additional data, for review and approval by the full RAC based on the following: (1) failure of the primary reviewers to recommend approval of the protocol, (2) lengthy delays that have 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 has requested the use of a substitute vector. If Dr. Roth submits a revised protocol, new primary reviewers will be assigned. The consensus of the RAC is that the protocol is considered administratively inactivated; therefore, RAC approval of the protocol is withdrawn. The RAC recommended that ORDA forward a letter to Dr. Roth outlining consensus of the RAC.

XVII. ADDITION OF APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GEN TRANSFER PROTOCOL ENTITLED: ADOPTIVE IMMUNOTHERAPY OF MELANOMA WITH ACTIVATED LYMPH NODE CELLS PRIMED IN VIVO WITH AUTOLOGOUS TUMOR CELL TRANSDUCED WITH THE IL-4 GENE/DR. CHA*

Review--Dr. Geidusche

Dr. Walters called on Dr. Geiduschek to present his primary review of the protocol submitted by Alfred E. Chang of the University of Michigan, Ann Arbor, Michigan. Dr. Geiduschek explained t this protocol is an extension of an ongoing non-gene transfer adoptive immunotherapy protocol for renal cell carcinoma and melanoma in which patients are vaccinated with their own tumor cells that have been lethally irradiated, mixed with BCG (Bacille Calmette -Guerin) adjuvant, an in the vicinity of lymph nodes, which are subsequently removed. Lymphocytes from these excised lymph nodes are stimulated by exposure to a monoclonal anti-CD3 antibody and expanded in the presence of IL-2 to yield a large population of antitumor effector T cells. The latter are reintr into patients with concurrent IL-2 administration. Dr. Chang reported a significant response to this procedure in renal cell carcinoma patients with a lesser response observed in melanoma patients. This gene transfer protocol is intended to address melanoma because of the decreased response to adoptive immunotherapy.

Dr. Geiduschek explained that this proposal attempts to up-regulate the immunogenicity patients' tumor cells through enhanced IL-4 expression by transduction with the GBAH4-18 retroviral vector. Fifteen patients with advanced melanoma will be entered into this protocol. The objectives of this study are to: (1) assess the feasibility of transducing patients' tumor cells wit the IL-4 gene and assess toxicity, (2) evaluate antitumor efficacy *in vivo* immunological responses, and (3) evaluate the immunological reactivity of activated lymph node cells *in vitro*. There have been disappointing results obtained from the murine studies; no significan improvement was observed with IL-4 expressing cells. Dr. Geiduschek posed the followin questions. What is the rationale for using the chicken actin promoter for expression of the IL- gene? Optimal and sustained IL-4 production has not been demonstrated using patient tumor cells. Is there *in vitro* data available that demonstrates the immunological reactivity of these transduced cells? Have any differences been observed between lymph node cells stimulated w untransduced tumor cells versus IL-4 transduced cells? Although the PI has responded to s of the concerns raised by the primary written review, the protocol is too premature to recommend

approval. However, if the RAC does recommend approval of this protocol, there should be stipulations to address the technical shortcomings of the study.

Review--Dr. Motulsky (presented by Dr. Geidusch

Dr. Geiduschek summarized Dr. Motulsky's written comments. This approach has biolo plausibility and appears feasible. The treatment schema is complex and requires considerable manipulation of tumor cells, patient immunization, preparation of lymphocytes from lymph nodes, and IL-2 administration. Since the investigators have previously demonstrated success with an analogous non-gene therapy approach, this study is justified and could result in improved tumor therapy. The Informed Consent document is appropriate. Since there are no new risks associated with the gene manipulation aspects of this study, the protocol should be approved by the RAC.

Review--Ms. Meyers

Ms. Meyers' concerns focused primarily on the Informed Consent document. The investigators have adequately responded to initial concerns regarding the use of the term "tumor vaccine," recommendations for male/female contraception, and patients' responsibility for research-related costs; therefore, the revised Informed Consent document is acceptable.

Investigator's Responses--Drs. Chang and Kraus

Dr. Chang responded to the RAC's questions about preclinical data and stated that hi co-investigator, Dr. Kraus, will address the RAC's questions about the proposed vector an transduction procedures.

Responding to the comments raised by Dr. Geiduschek , Dr. Chang said that in their ow interpretation, the animal data demonstrates increased immunogenicity in response to IL- transduced lymphocytes compared to untransduced cells. Similar results have been obtai using another IL-4 expressing vector construct. Dr. Chang stated that Dr. Geiduschek's comparison between IL-4 and BCG is not pertinent for this human trial because a different and more potent bacterial adjuvant, *C. parvu*, was used for the murine studies. Although th response with IL-4 transduced cells was similar to results obtained wit *C. parvu*, IL-4 transduced cells were more effective than untransduced tumor cells alone. The animal d demonstrated an antitumor response for established tumors. For this reason, the animal studie provide sufficient justification for the proposed human clinical trials.

In response to Dr. Geiduschek's questions about immunological assays, Dr. Chang said tha immune reactivity of draining lymph node cells will be determined by cytolytic activity, cel proliferation, and cytokine release. An autologous tumor cell delayed skin test will be used t determine the *in vivo* response.

Dr. Parkman inquired about the number of animals used for the animal studies. Dr. Chang said tha an extensive murine experiment was conducted involving 70 mice (5 mice in each experimenta group). This animal model is being used to define the most pertinent assays for the human study.

Dr. Geiduschek reiterated his reservations about the interpretation of the murine experiment Dr. Chang has agreed that the experiment did not demonstrate an improved immune response using IL-4 transduced cells over the bacterial adjuvant, i.e. *C. parvu*, the animal data do not provide justification for the human study. Dr. Leventhal stated that the investigators should not

penalized for results that indicate that IL-4 therapy is equivalent to the best bacterial adjuvant therapy. Since IL-4 and BCG stimulate the immune system by different mechanisms, th combination of these two stimulants may yield a synergistic effect. Dr. Parkman cautioned that the animal data cannot be directly extrapolated to the human study. The relative potency of IL-4 and bacterial adjuvants may be different in humans; however, it is unnecessary to demonstrate tha IL-4 is a more effective stimulant to justify the human study. Patients should have the option to choose the clinical protocol in which they desire to participate. Dr. Leventhal added that BCG *C. parvu* are very complex bacterial adjuvants , and IL-4 is a less complex protein; therefore scientific interpretation of the IL-4 data would be less complicated. Dr. Chang presented additional murine data to substantiate his assertion that IL-4 transduced cells elicit an enhan immunologic response as compared to untransduced cell

Dr. Kraus answered the RAC's questions about tumor cell transduction. Most of the experiment have been performed using late passage melanoma cells rather than early passage cells, which are more relevant to the human study. Dr. Geiduschek suggested the RAC might condition it approval on optimization of the transduction efficiency and IL-4 production. Dr. Kraus agreed to accept a minimum production level of 50 picograms (pg) of IL-4/106 cells/ml/24 hour

Dr. Leventhal suggested the inclusion of a stopping rule that if the investigators are unable t transduce cells at the minimum level of IL-4 production in 3 of the first 6 patients, the investigat are not permitted to treat any additional patients until they return to the full RAC for discussion of the data. Dr. Chang said that a range of IL-4 expression would allow for a dose-response assessment. Dr. Parkman responded that a 10-fold lower level of IL-4 expression resulted in antitumor responses in the animal model; therefore, the level of IL-4 secretion stipulated by Dr Geiduschek is acceptabl
Committee Motion

A motion was made by Dr. Leventhal and seconded by Dr. Carmen to approve the protocol Approval of the protocol is contingent on submission of the following: (1) data demonstrating optimization of cell transduction in early passage human melanoma cells and a minimum level of IL-4 secretion (50 pg of IL-4/106 cells/ml/24 hours), and (2) inclusion of a stop criterion that if the investigators are unable to transduce cells at the minimum level of IL-4 secretion in 3 of the firs patients enrolled in the study, the investigators will not be permitted to treat additional patients without returning to the full RAC for discussion of the data. The motion to approve the protocol passed by a vote of 12 in favor, 3 opposed, and 1 abstention.

XVIII. UPDATE ON THE HUMAN GENE TRANSFER PROTOCOL ENTITLED: *A PHASE I STUDY, IN CYSTIC FIBROSIS PATIENTS, OF THE SAFETY, TOXICITY, AND BIOLOGICAL EFFICACY OF A SINGLE ADMINISTRATION OF A REPLICATION-DEFICIENT RECOMBINANT ADENOVIRUS CARRYING THE cDNA OF THE NORMAL HUMAN CYSTIC FIBROSIS TRANSMEMBRA CONDUCTANCE REGULATOR GENE IN THE LUNG/DR. CRYSTAL*

Dr. Crystal presented a progress report on his ongoing CF protocol. He stated that the CFTR ge has been successfully delivered to the airway epithelium using an E1- and E3-deleted adenovirus vector. Both *in vitro* and *in vivo* expression of the CFTR gene has been demonstrated. Possibl safety concerns are over-expression of the inserted gene, inflammation, immune reactions, generation of replication-competent virus, complementation, recombination, germ line transfer, and virus shedding. In animal studies involving rhesus monkeys, doses ranging between 10 and 100 times of those doses proposed for the human study demonstrated no acute or chronic clinical sequelae . Four patients have been treated on the human study to date. No adverse reactions w

encountered with intranasal administration of the vector in any of these patients. These patients underwent delivery to the lower lobe of one side of the lung by a fiberoptic bronchoscope. On patient received a dose of 2 x 106 cfu , 2 patients received 2 x 107 cfu , and 1 patient received 109 cfu

There was no evidence of shedding of replication-competent adenovirus from any of the treated patients. A dose-dependent induction of complement fixation antibodies was demonstrated; however, no induction of neutralizing antibodies was observed in treated individuals. Patient 2A, who received the highest concentration of vector, developed a mild reaction. This 24 year-old female received a dose of 2 x 107 cfu to the nasal epithelium, and 24 hours later she received 2 109 cfu to the right lower lobe bronchus. She exhibited symptoms of fatigue for 5 to 7 days intermittent fever for 6 days, hypotension, hypoxemia, and lung infiltrate in the right lower and middle lobes. Although the vector was administered to the lower lobe, infiltrate in the right middle lobe was confirmed by a chest X-ray. All reactions were transient and disappeared after symptomatic treatment. The single adverse effect was probably due to vector-induced inflammation of the lung. Other possible causes have been eliminated, such as pathology of the disease itself, complication of bronchoscopy , contamination of the vector preparation, an complementation or recombination of vector with other adenovirus strains. No adverse reactions were observed in the preclinical animal studies.

The efficacy data are incomplete at this time. CFTR gene expression was demonstrated in th nasal epithelium; however, functional data demonstrating correction of the CFTR deficiency in nasal epithelium are suggestive but less conclusive. The present data defines a range of toxicity that will allow for the design of future experiments. Lower starting doses will be initiated in order t explore a dose range that will prove to be efficacious.

Dr. Miller asked whether any adverse reactions were observed in the monkeys following repeat vector administration. Dr. Crystal responded that no responses were observed in monkeys. These reactions may be specific to CF patients whose lungs already have abnormalities. Dr. Crystal explained that the volume of the vector has been reduced from 20 ml to 5 ml for lung administration to avoid the possibility of alveolar inflammation. The adverse event was reported to the RAC, IRB , FDA, and other investigators conducting CF gene transfer trials. Similar dos adjustments have been made in other CF trials.

XIX. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING HUMAN GENE TRANSFER PROTOCOL ENTITLED: GENE THERAPY FOR CYSTIC FIBROSIS USING CATIONIC LIPOSOME MEDIATED GENE TRANSFER: A PHASE I TRIAL OF SAFETY AND EFFICACY IN THE NASAL AIRWAY/DRS. SORSCHER AND LOG*

Review--Dr. Post

Dr. Walters called on Dr. Post to present his primary review of the protocol submitted by Drs. Eric J. Sorscher and James L. Logan of the University of Alabama, Birmingham, Alabama. Dr. Pos explained that the objective of this proposal is to evaluate cationic liposome-based delivery of the CFTR gene to nasal respiratory epithelia of CF patients. The nasal airway epithelium is an idea model for gene transfer since this epithelium exhibits a CF bioelectric defect and is easily accessible for safety and efficacy studies. The study will utilize 3 ascending dosages of CFTR cDNA . Each patient will receive CFTR /liposome administration to one nostril and a m transfection (lipid with DNA lacking CFTR) of the contralateral nostril as a control. The pr DNA delivery system differs from the other CF protocols previously reviewed by the RAC. As

noted previously by Dr. Crystal, there may be limitations to using the adenovirus vector; therefore, it is reasonable to investigate more than one gene delivery approach. Another cationic liposome CFTR protocol has been already initiated in the United Kingdom. In his initial review, Dr. Pos requested the investigators to provide safety or efficacy data using the proposed cationic liposome, DMRIE /DOPE. The majority of the preclinical data was obtained using another lipid DOTMA /DOPE, N-[1-(2,3-dioleoyloxypropyl)]-3-trimethylammonium-propane) dioleoylphosphatidylethanolamine . Although the investigators might argue that the RAC ha previously approved the DMRIE /DOPE system for Drs. Nabel and Rubin's studies, intranasal delivery to healthy CF patients raises safety issues different from those posed by intratumoral injection of terminally ill melanoma patients. The investigators have submitted additional data to demonstrate safety of the liposome and expression of a reporter gene in a rat model. These data are still too preliminary to justify approval of the human study. The investigators have outlined several ongoing safety experiments in the rat model involving short-term and long-term toxicity of the DMRIE /DOPE/ CFTR construct. The strategy and preliminary data appear reasonab Therefore, he recommended RAC approval of the protocol contingent on submission of data from these ongoing animal experiments.

Dr. Post asked the investigators to respond to several other questions. Where does the 1 ml volume of the DNA/liposome mixture go after intranasal administration? Would a device designed to prevent nasal drainage be useful? Does the DNA integrate into chromosomes? What is the expected duration of gene expression using this method of delivery? In response to a previous suggestion by Dr. Miller, the investigators have deleted an open reading frame encoding 44 amino acids from the carboxy terminus of the SV40 small T antigen of the pKCTR vector. Has t modification been incorporated into the control vector?

Dr. Walters asked whether the liposome delivery method poses less of a public health concern than adenovirus vector delivery? Dr. Post answered that liposome delivery presents a lesser degree of risk.

Review--Dr. Krogsta

Dr. Krogstad asked about the investigators' degree of confidence, from an anatomic an functional point of view, that the liposome material will remain in the nostril. Could fluorescein used diagnostically to answer this question? What is the level of sensitivity of the bioelectric potentiometric assay for the detection of CFTR expression? Is this assay sensitive enough detect differences between the treated and untreated nostrils? Based on Dr. Crystal's results, detection of CFTR expression is not a trivial problem. What are the possible risks associated w liposome delivery of CFTR to the nasal epithelium? Can the knowledge gained from this trial b successfully translated into a therapeutic treatment for CF? From a mechanical point of view, what is the degree of difficulty that might be encountered when administering this material throughout the tracheobronchial tre

Review--Dr. Secund

Dr. Secundy stated the following concerns about the Informed Consent document. This docume states that patients should not become pregnant; however, an adequate explanation about the possible risks has not been provided. Due to the duration of this disease, CF patients may be more likely to become pregnant than other terminally ill patients; therefore, pregnancy is an important issue. If a patient becomes pregnant and withdraws from the study, who will provide patient follow-up?

Other Comments

Ms. Grossman commented on the technical problems of measuring the potentiometric differenc between the treated nostril and the control nostril. This problem has not been adequately addressed by the investigators. Dr. Parkman asked about the recommended period for contraception since the risk of germ line gene insertion is unknown. Dr. Miller responded that there is minimal risk of germ line integration with local administration; therefore, contraception should not be required. Dr. Miller explained that the 44 amino acid coding sequence of the SV40 small T antigen at the polyadenylation site of the vector construct is unlikely to encode a gen product with transforming activity. Since the plasmid vector is not a virus, there is very little risk o replication and transmission to other individuals.

Investigator Response--Dr. Sorsche

Dr. Sorscher presented a diagram of the vector construct demonstrating that the small region o SV40 T antigen has been removed from the modified DNA construct.

In response to the RAC's concerns about the ability to measure nasal bioelectric potentia differences, the proposed techniques yielded consistent measurements. This procedure involves minimal discomfort to the patients. Consistently, 2- to 3-fold differences have been detected between the nostrils of CF patients and normal individuals. Therefore, correction of the CFTR defect should be measurable. Dr. Krogstad suggested that fluorescein could be used as a m to monitor the amount of material that crosses to the other nostril by ciliary activit

With regard to the issue of contraception, Dr. Sorscher said the risk of germ line integration is v small since this construct is not a viral vector; however, the risk will be clearly stated in the Informed Consent document. Since the risk is minimal, the contraception requirement will be deleted.

Dr. Miller asked whether inclusion of the ampicillin -resistance gene in the vector construct coul compromise the treatment of pneumonia in CF patients? Dr. Sorscher responded that there ar many other more useful antibiotics available. Ampicillin is not the antibiotic of choice for th treatment of pneumonia.

Ms. Meyers recommended that a letter be sent to Dr. Sorcher's IRB requesting that the state about compensation for research-related injury be deleted from the Informed Consent document.

Committee Motion

A motion was made by Dr. Post and seconded by Dr. Secundy to approve the protocol continge on the submission of data derived from the ongoing toxicity studies as outlined in Dr. Sorscher's response to Dr. Post dated December 2, 1993. The motion to approve the protocol passed by a vote of 15 in favor, 0 opposed, and 1 abstention.

The RAC recommended that a letter be sent to the University of Alabama's IRB requesting delet of the following paragraph from the *Special Risks and Discomfort Related to Being Part of a Study of Gene Administration* section of the Informed Consent document:

"(b) Throughout the study I will continue to be monitored for complications which are normally

associated with CF. Should any of these complications develop, I will be given appropriate therapy. If the complications do not appear to be related to the gene transfer protocol, the usual means of payment (for example, insurance) should be arranged. The University of Alabama, Birmingham, and the Children's Hospital of Alabama have made no provision for monetary compensation in the event of physical injury resulting from research and in the event of such injury, medical treatment is provided, but is not provided free of charge."

XX. ADDITION TO APPENDIX D OF THE *NIH GUIDELINES REGARDING A HUMAN GEN TRANSFER PROTOCOL ENTITLED: ADENOVIRUS-MEDIATED GENE TRANSFER OF CFTR T THE NASAL EPITHELIUM AND MAXILLARY SINUS OF PATIENTS WITH CYSTIC FIBROSIS/DR. WELSH*

Review--Dr. Post

Dr. Walters called on Dr. Post to present his primary review on the protocol submitted by Dr. Michael J. Welsh of Howard Hughes Medical Institute, Iowa City, Iowa. Dr. Post stated that this protocol is an extension of Dr. Welsh's first RAC approved protocol in which an adenovirus- CFTR vector was administered to the nasal epithelium of CF patients. This current proposal involves the multiple administration of increasing doses of a new vector to the nasal epithelium as well as the maxillary sinus. Safety of the modified dosing schedule will be demonstrated in the nasal epithelium prior to maxillary sinus administration.

Dr. Post noted that the results obtained from Dr. Welsh's previous trial are promising. Gene transfer for CF is an excellent example of different investigators using separate approaches that provide informative results. These trials complement each other. The documentation submitted in support of this proposal is superb. Dr. Post commended the investigators for providing a thorough report on the results of the first trial. Data from the cotton rat experiments indicate that large doses of the adenovirus vector can cause inflammation. This *in vivo* data, in addition to Dr. Crystal's report on a possible adverse effect, supports the strategy of characterization of these vectors in the upper respiratory tract prior to lung administration.

Dr. Post stated that the investigators provided excellent responses to the questions presented in his primary review. He asked the investigators to respond to the following additional comments: (1) The investigators propose to use a new adenovirus vector in which a PGK (phosphoglycer kinase) promoter is used to permit sustained low level CFTR expression. Is there any evide that the limited duration of CFTR expression with the previous vector is due to promoter shut-o as opposed to loss the vector DNA? (2) The investigators state that the possibility of recombination of the new types of adenovirus sequences with the 293 vector producer cells is lower than with the new vector than the previous vector. Has the new vector been subjected to the same level of safety testing as the previous vector? (3) In what volume will the vector be administered to the nose versus the maxillary sinus? Have any precautions been introduced to prevent spillage? Dr. Welsh responded that 0.5 ml will be used. The maxillary sinus is self contained; therefore, spillage is not a significant problem. (4) Have preclinical experiments been conducted demonstrating the ability to administer the vector to the maxillary sinus? (5) The investigators have stated that patients with active adenovirus shedding within 3 weeks will be excluded from the study to avoid recombination with wild-type virus. What is the exact period of time indicated by this statement? Dr. Welsh responded that patients demonstrating positive adenovirus cultures 3 weeks prior to the start of the experiment will be excluded from the study. (6) When and how after will biopsies be performed? (7) The subjects will be isolated for 24 hours following vector administration based on the previous observation that virus shedding was

absent after this period of time. However, this proposal involves a 200 fold increase in the amount of virus administered. Will this period of isolation be adequate for these increased doses? Dr. Welsh responded that isolation periods greater than 24 hours may be detrimental to CF patients. CF patients must maintain a daily exercise routine. Dr. Post agreed that lack of exercise is a reasonable consideration, but cautioned that the monitoring of virus shedding is an important safety issue. However, it is most likely that the recombinant vector does not pose increased risk over the wild-type virus. (8) What proportion of each vector lot will be assayed for wild-type adenovirus? Dr. Welsh has indicated his intention to request permission to introduce the same promotor used in this vector, PGK , into other adenovirus vectors as outlined in the protoc These changes would be submitted to the RAC as minor modifications to the current proposal. Dr. Post stated that he would recommend approval of such modifications.

Review--Dr. DeLeo

Dr. DeLeon complimented the investigators on this well-documented protocol. The rationale an schema for the proposal is logical, the end points are clearly defined, and complete responses to the *Points to Consider* have been provided. The investigators propose to use a modified adenovirus vector construct for which safety and efficacy have been addressed in the preclinical animal studies. Several minor changes should be made to the Informed Consent document. Since this protocol is a Phase I/II study, the term "treatment" should be replaced with the word "procedure," and the term "gene therapy" should be replaced by "gene transfer." Patients should be informed that a determination will be made whether they are seropositive to adenovirus. Sin this protocol is well presented and all of her original concerns have been adequately addressed, Dr. DeLeon recommended approval of this proposa

Review-- Mr . Capron (presented by Dr. DeLe

Dr. DeLeon summarized Mr. Capron's written review. The protocol was well-presented. Severa minor issues concerning the vector construct have been adequately addressed by the investigators. The number of patients to be enrolled on this study is reasonable and will be limited to those individuals who are seropositive to adenovirus. This criterion will facilitate a rapi immune response and minimize risk of virus transmission. Two separate Informed Consent documents have been approved by the IRB , one document for the nasal epithelium study an another document for the maxillary sinus study. Both of these Informed Consent documents are complete, well presented, and understandable to laypersons.

Other Comments

Ms. Grossman said that the investigators have stated that there were several animal deaths in the preclinical studies. Why was the cause of death undetermined? The investigators need to provide an explanation as to why little differences were observed between single and multiple vector administration in the animal studies. Why was mild inflammation observed in animals at multiple high doses of vector? The RAC must decide whether an open ended vector modification should be approved for this study since significant changes in vectors may affect the immunological responses. The investigators should elaborate on their request to decrease the patient isolation period to 24 hours.

Dr. Post suggested that a reasonable compromise regarding the proposed vectors would be for the RAC to approve the use of the previously approved vector (AD2/CFTR-1) as well as the proposed vector (AD2-ORF6/ PGK-CFTR). Any future vector modifications should be submitted

requests for minor modifications.

Dr. Leventhal noted that the highest proposed dose, 1010 cfu , is a higher dose of adenovirus the dose that resulted in the adverse effect reported by Dr. Crystal. Dr. Parkman stated that the RAC may want to reconsider the proposed isolation period for the maxillary sinus administration arm of the study since the vector may persist for a longer period in this isolated area. Ms. Meyers stated that the Informed Consent document does not include recommendations for male contraception, period of contraception, long-term follow-up, and responsibility for costs associated with research-related injury.

Investigator Response--Dr. Welsh

Dr. Welsh responded to the RAC's concerns about the patient isolation period. Patients wer isolated for 5 to 6 days in the previous study. This period of time presented several serious problems to the CF patients. Their clinical symptoms were adversely affected by their lack of daily exercise. Patient recruitment was difficult due to the reluctance of these patients to remain in the hospital for almost one week a month while enrolled in the protocol. A prolonged isolation period is unnecessary because these vectors are replication-deficient. In addition, the proposed new vector contains an E4 deletion that limits its survival outside of the patient's body. Despite the extensive use of these vectors in many laboratories, there have been no instances of adverse consequences to laboratory personnel or health care workers. In an unrelated study in which army personnel were inoculated with wild-type adenovirus, the rate of horizontal transmission in these subjects was extremely low. Other investigators have published monkey studies in which a low rate of horizontal transmission was demonstrated. At a previous RAC meeting, Dr. Harold Ginsberg of Columbia University (an *ad hoc* reviewer for the initial CF studies) indicated that the chance of these impaired viruses surviving outside of the clinical setting is extremely low. The IR has included the requirement that health care workers will be assayed for immunologic responses to these viruses.

Ms. Grossman asked if the proposed vector poses little risk, why will patients be isolated for 24 hours? Dr. Welsh responded that this time period is for the purpose of patient observation. Dr. Miller commented that the half-life of the virus, approximately 2 minutes at 46o C *ex vivo*, is relatively short; therefore, a short isolation period is justified. Dr. Welsh said that complete vector clearance was observed within one day in the previous study. Dr. Miller suggested that the RAC approve the protocol contingent on the stipulation that if virus is detected within 24 hours in a single patient, the isolation period should be extended. Although there are no major safety concerns associated with adenovirus shedding, the RAC should maintain public confidence about gene transfer studies by ensuring the lack of virus shedding. Ms. Grossman stated that although she has provided comments regarding the proposed study, she will abstain from voting on the protocol due to conflict of interest (co-investigator on another RAC-approved CF protocol).

Dr. Welsh said that the unexplained death of some animals in the preclinical studies was unrelated to gene therapy, noting that the control animals developed symptoms. All animals (male and female) were from a single lot of animals. If the new PGK promoter proves to be more efficaciou than the previous promoter, a request for a minor modification will be submitted as suggested by Dr. Post.

In response to Ms. Grossman's question about the lack of difference in gene expression between single versus multiple vector administration in cotton rats, Dr. Welsh explained that the context of the experiment was misunderstood. In monkey experiments, the same level of expression of the

reporter gene was observed even after 5 administrations of the vector. The present study is to test toxicity associated with multiple dosing of the vector.
Dr. Welsh responded to the question of vector-induced inflammation. The data derived from animal and human experiments is variable. Variations have been observed between laboratories. Possible explanations for these variations are different vector constructs, different animal species or strains, and the purity of the vector preparations. Dr. Welsh presented data from his murine study in which vector purity affected the outcome of the experiment. At high doses, pure clinical grade vector preparations caused no evidence of inflammation; however, the lesser purity preparations caused peribronchial inflammation. Different animal species appeared to be variable factor, e.g., the inflammation observed in BALB /c mice was not present in C57/ Bl m

In regard to Informed Consent document issues, Dr. Welsh stated that contraception will be recommended for both females and males throughout the active phase of the study and for 1 month after this period. Dr. Chase recommended that a letter be sent to Dr. Welsh's IRB abou provision of compensation in the event of research-related injury.

Dr. Walters inquired about the degree of discomfort experienced by patients undergoing biopsy of their maxillary sinus. Dr. Scott Graham (an otolaryngologist and co-investigator on this protoco responded that biopsy of the maxillary sinus is a procedure commonly performed under local anesthesia. A slight degree of discomfort is associated with the procedure; however, the tissue obtained is crucial to understanding pathogenesis if an adverse reaction is encountered.

Committee Motion

A motion was made by Dr. Post and seconded by Dr. DeLeon to approve the protocol with th following stipulations: (1) the investigator retains the option to use either the AD2-ORF6/ PGK-CFTR (new) or AD2/CFTR-1 (old) adenovirus vectors, and (2) patients will b isolated for a period of 24 hours following vector administration; however, if a single patient demonstrates virus shedding at 24 hours, the investigator will immediately notify the RAC for reconsideration of the isolation period. The motion to approve the protocol passed by a vote of 11 in favor, 1 opposed, and 3 abstentions.

The RAC recommended that a letter be sent by ORDA to the IRB of the University of I requesting that the following statement be deleted from the Informed Consent document:

"I understand that in the event of physical injury resulting directly from the research procedures, no compensation will be available in the absence of negligence by a state employee. However, medical treatment is available at the University Hospitals and Clinics, but I will be responsible for making arrangements for payment of the expenses of such treatments..."

XXI. AMENDMENTS TO SECTIONS III, IV, V OF THE *NIH GUIDELINES AND THE POINTS T CONSIDER REGARDING NIH (ORDA) REVIEW AND APPROVAL OF CERTAIN CATEGORIES HUMAN GENE TRANSFER EXPERIMENTS THAT QUALIFY FOR THE ACCELERATED REVIEW PROCESS/DR. PARKMAN*

Dr. Parkman, Chair of the RAC Working Group on Accelerated Review provided a summary of the proposed amendments to the *NIH Guidelin*and *Points to Consider* regarding accelerated review of human gene transfer protocols. The proposed amendments would: (1) establish an accelerated review process for ceratin categories of human gene transfer experiments (i.e., "umbrella" mult site protocols in which the PI is responsible for quality control and data reporting for research

conducted at all sites, duplicate protocols conducted at sites other than those originally approved by the RAC and in which there is a new PI, protocols involving lethally irradiated cells with no replication-competent virus, and modifications to previously approved protocols not related to gene transfer); (2) allow the NIH (ORDA) to assign the appropriate review category to all hu gene transfer proposals that are submitted in compliance with *NIH Guidelin*; (3) allow NIH (ORDA) to approve those categories of human gene transfer experiments that qualify for th accelerated review process in consultation with the Chair and one or more RAC members, as necessary; and (4) exempt certain experiments involving the transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into one or more human subjects which are not covered by Footnote 21. All human gene transfer experiments approved by NIH (ORDA) through accelerated review process would be provided in a report by the Chair at the next regularly scheduled RAC meeting and included in the list of approved experiments which is available form ORDA . Experiments approved through the accelerated review process would be considered *Minor Actions* to the *NIH Guidelin*, eliminating the necessity for full RAC review and publication of the proposed action in the *Federal Register*. Human gene transfer experiments that are not considered as *Minor Actions* or *Exempt* from the *NIH Guidelin* would be considered *Major Actions*, and require publication in the *Federal Register*, full RAC review, and approval by the NIH Director.

Committee Consensus

The consensus of the RAC was that this proposal should be published for public comment in the *Federal Register* and reviewed at the next regularly scheduled RAC meeting.

XXII. ADJOURNMENT

Dr. Walters adjourned the meeting at 4:45 p.m. on December 3, 1993.

Nelson A. Wivel , M.
Executive Secretary

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

LeRoy B. Walters, Ph.
Chair
Recombinant DNA Advisory Committee
National Institutes of Health