RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting
September 12, 1997

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

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The Recombinant DNA Advisory Committee (RAC) was convened for its sixty-eighth meeting at 9:00 a.m. on September 12, 1997, at the National Institutes of Health (NIH), Building 31, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Claudia Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on September 12 from 9 a.m. until 4:30 p.m. The following were present for all or part of the meeting:

Committee Members:

C. Estuardo Aguilar-Cordova, Texas Childrens Hospital
Dale G. Ando, Cell Genesys, Inc.
Jay J. Greenblatt, National Institutes of Health
Jon W. Gordon, Mt. Sinai School of Medicine
Eric T. Juengst, Case Western Reserve University
Michael M.C. Lai, University of Southern California
M. Therese Lysaught, University of Dayton
Ruth Macklin, Albert Einstein College of Medicine
M. Louise Markert, Duke University Medical Center
R. Scott McIvor, University of Minnesota
Claudia A. Mickelson, Massachusetts Institute of Technology
Karen Rothenberg, University of Maryland School of Law
Jon A. Wolff, University of Wisconsin Medical School

Executive Secretary:

Debra W. Knorr, National Institutes of Health

Non-Voting Representatives:

Philip Noguchi, Food and Drug Administration

National Institutes of Health staff:

Bobbi Bennett, OD
Jan Casadei, NCI
Joseph Gallelli, OD
Christine Ireland, OD
Becky Lawson, OD
Mikel Miller, OD
Gene Rosenthal, OD
Thomas Shih, OD
Atsushi Watanabe, NIDCD

Others:

Victoria Allgood, GeneMedicine, Inc.
Robert Anderson, Food and Drug Administration
W. French Anderson, University of Southern California
Bridget Binko, Cell Genesys, Inc.
Andrew Braun, Massachusetts General Hospital
Jeff Carey, Genetic Therapy, Inc.
Lucetta Caston, Introgen Therapeutics, Inc.
Ronald Crystal, Cornell University
Kenneth Culver, Codon Pharmaceuticals, Inc.
Dean Engelhardt, Enzo Biochem, Inc.
Diane Fleming, Consultant
Jerry Gottlick, U.S. Medicine
Tina Grasso, GenVec
Tanya Houle, Genzyme Corporation
Dorothy Jessop, Public
Daniel Jones, U.S. Department of Agriculture
Leonard Kapcala, Genetic Therapy, Inc.
Yoshihiro Kitamura, National Institute of Infectious Diseases, Japan
Steven Kradjian, Vical, Inc.
LaVonne Lang, Warner-Lambert Parke-Davis
Sheryl Osborne, NeuroVir, Inc., Canada
Sara Radcliffe, SmithKline Beecham Pharmaceuticals
Joseph Rokovich, Pangaea Pharmaceuticals, Inc.
Tomiko Shimada, Ambience Awareness International, Inc.
Dominick Vacante, Magenta Corporation
Lisa White, The Blue Sheet
Chester Whitley, University of Minnesota

I. CALL TO ORDER AND OPENING REMARKS/DR. MICKELSON

Dr. Claudia A. Mickelson, Chair of the Recombinant DNA Advisory Committee (RAC), called the meeting to order and stated that due notice of the meeting and the proposed actions under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* were published in the *Federal Register* on August 20, 1997 (62 FR 44387). She noted a quorum was present and stated the order in which speakers would be recognized: (1) primary reviewers, (2) other RAC members, (3) *ad hoc* experts, (4) responses from the principal investigators (PIs), (5) other NIH and Federal employees, (6) the public who have submitted written statements prior to the meeting, and (7) the public at large.

Dr. Mickelson welcomed the new RAC members: Dale G. Ando, M.D., Vice President, Clinical Department, Cell Genesys, Inc., Foster City, California; Jay J.Greenblatt, Ph.D., Head, Drug Regulatory Affairs Section, Division of Cancer Treatment, Diagnosis, and Centers, National Cancer Institute, NIH, Bethesda, Maryland; Jon W. Gordon, M.D., Ph.D., Professor, Departments of Neurobiology and OB/GYN, Mount Sinai School of Medicine, New York, New York; Eric T. Juengst, Ph.D., Associate Professor, Center for Biomedical Ethics, Case Western Reserve University, Cleveland, Ohio; and Ruth Macklin, Ph.D., Professor of Bioethics, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, New York.

Dr. Mickelson noted two recent examples of interagency collaboration between the Food and Drug

Administration (FDA) related to gene therapy research: (1) *Forum 1997: Gene Therapy*, a conference jointly sponsored by the National Cancer Institute, NIH, and the Center for Biologics Research Evaluation, FDA, that was held July 15-18, 1997, in Bethesda, Maryland. Dr. Mickelson emphasized the importance of future participation by RAC members in this forum. (2) A June 30, 1997, letter from Dr. Mark Elengold, FDA, to Dr. Lana Skirboll, Associate Director for Science Policy, NIH, regarding submission of human gene transfer research-related Investigational New Drug (IND) applications to the FDA. Dr. Elengold's letter detailed FDA's intention to transmit the following IND-related information to the NIH Office of Recombinant DNA Activities (ORDA): (i) date of receipt, (ii) study title, (iii) sponsor, and (iv) principal investigator(s). Transmittal of such information will allow NIH/ORDA to contact sponsors and investigators of human gene transfer protocols for the purpose of ensuring compliance with Appendix M-I, *Submission Requirements -- Human Gene Transfer Experiments*, of the *NIH Guidelines*. Dr. Mickelson noted that relevant IND application information would not be disclosed to anyone other than NIH/ORDA staff, IND sponsors, and principal investigators.

Dr. Mickelson noted two letters received in response to the proposed actions published in the *Federal Register* on August 20, 1997. (1) In a letter dated September 10, 1997, from Dr. Joseph VanHouten, President of the American Biological Safety Association, it states that the items mentioned in the proposed actions are of concern to a number of the Association members. The Association would like to have an opportunity to comment on the proposed actions and would request to extend the comment period by 60 days to allow sufficient time for the Association to convene a subcommittee to consider these issues. (2) In a letter dated September 8, 1997, from Dr. Alexander E. Kuta, Director of Regulatory Affairs, Genzyme Corporation, it stated that Genzyme disagreed with the motion to incorporate the responses to Appendix M-II through M-V of the *NIH Guidelines* into the clinical protocol stating, "this action would compromise the integrity of the clinical protocol without sufficiently addressing industry's concerns regarding Appendix M. The clinical protocol...should be 'directed primarily at providing an outline of the investigation.'"

II. MINUTES OF THE JUNE 12-13, 1997, MEETING/WOLFF AND LYSAUGHT

Committee Motion 1

The RAC approved a motion made by Dr. Lysaught and seconded by Dr. Juengst to accept the minutes of the June 12-13, 1997, RAC meeting (with the incorporation of minor editorial changes), by a vote of 11 in favor, 0 opposed, and no abstentions.

III. UPDATE ON DATA MANAGEMENT/GREENBLATT

Dr. Greenblatt noted that a total of 204 protocols have been registered with NIH/ORDA to date: (1) 30 gene marking; (2) 173 gene therapy (119 cancer, 30 monogenic diseases, 20 human immunodeficiency virus (HIV)/AIDS, and 4 other diseases/disorders); and (3) 1 non-therapeutic (to study immune response to adenovirus vectors in normal subjects). He stated that 19 of these protocols were submitted after the June 12-13, 1997, RAC meeting. Of these 19 recent submissions, the RAC recommended that 12 protocols should be solely reviewed by the FDA and 7 protocols are currently under review.

Dr. Greenblatt noted that 17 protocol amendments and 3 safety reports/adverse events were submitted since the June 12-13, 1997, RAC meeting. He stated that two specific amendments should be noted: (1) Protocol #9701-173, *A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^5-Methylguanine DNA Methyltransferase*, Dr. David Williams, Indiana University School of Medicine, Indianapolis, Indiana. This amendment involved a

change of vector from PKG-MGMT to MSCV-MGMT. The investigator explained that the reason for this requested modification was that replication-competent retrovirus (RCR) had been detected with PKG-MGMT. Dr. Greenblatt recommended that NIH/ORDA should request that the investigators provide additional information regarding: (a) the RCR detection method; and (b) and level of RCR detected. (2) Protocol #9701-171, *Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector ($AD_{GV}CD.10$) in Normal Individuals*, Drs. Ben-Gary Harvey and Ronald Crystal, Rockefeller University Hospital, New York, New York. Dr. Greenblatt explained that this amendment would be discussed in further detail by the RAC during this meeting.

Dr. Greenblatt stated that the following safety reports/adverse events should be noted: (1) Protocol #9209-026, *A Study of the Safety and Survival of the Adoptive Transfer of GeneticallyMarked Syngeneic Lymphocytes in HIV Infected Identical Twins*, Dr. Robert Walker, National Institutes of Health, Bethesda, Maryland. The investigators concluded that the reported lymphoproliferative disorder most likely resulted from complications of HIV-1 infection and was not related to the gene transfer procedure. (2) Protocol #9610-164, *Phase I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases*, Drs. Max Sung and Savio Woo, Mt. Sinai Medical Center, New York, New York. The investigators reported a Grade I hematological event that was possibly related to ganciclovir administration.

Other Comments

Dr. Aguilar-Cordova suggested that it is unnecessary for the RAC to request additional information about the methodology used for RCR detection, because the FDA follows up on these issues. Dr. McIvor said that the investigators did not provide an explanation as to how the change in vector promoter elements would avoid future occurrence of RCR; he speculated that the packaging cell line change was relevant and should be explained further. Dr. McIvor noted that it would be useful for the investigators to provide an explanation regarding the rationale for the change in vector. Dr. Lysaught noted that follow-up on RCR detection is a safety issue within the RAC's purview. Dr. Greenblatt agreed. Dr. Philip Noguchi (FDA) suggested that the FDA could summarize the rationale for the vector change and provide this information to the RAC. Dr. Noguchi emphasized that any vector preparations in which RCR are detected cannot be used for human trials. Drs. Wolff and McIvor said that such information is valuable to the community using retroviral vectors. Dr. Mickelson suggested that ORDA write a letter to the investigators requesting further explanation of the rationale for the change of the vector. Dr. Gordon noted that the investigators should provide and explanation regarding the change in promoter.

Dr. Noguchi stated that the FDA has produced a preliminary guidance document related to the RCR testing and offered to present this information to the RAC at its next meeting. Dr. Aguilar-Cordova stated that the RAC has exempted most routine protocols, and it does not need to deal with the issue of a vector changes. Ms. Knorr noted that investigators are required to inform NIH/ORDA of all protocol modifications, including vector changes, in accordance with the *NIH Guidelines.* Dr. Gordon stated that a change in a promoter is a significant change, because gene expression will be affected. Dr. Mickelson recommended that NIH/ORDA should request that the investigator provide additional information on this promoter change, e.g., is increased gene expression expected?

Exempt Protocols since June 12-13, 1997, RAC Meeting

The 12 exempt protocols are listed as follows:

9704-185 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Melanoma Cell/Canarypox Virus/Cytokine/Interleukin-12 cDNA/Intratumoral Injection

Conry, Robert M., University of Alabama at Birmingham, Birmingham, Alabama;*Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding the Human Interleukin-12 Gene (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma.* Sponsor: NIH NCI-Cancer Therapy Evaluation Program.

NIH/ORDA Receipt Date: 4-1-97. Sole FDA Review Recommended by NIH/ORDA: 7-2-97

9704-186 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Cationic Liposome Complex/EDMPC/Intranasal Administration

Noone, Peadar G. and Knowles, Michael R., University of North Carolina at Chapel Hill, North Carolina; *A Double-Blind, Placebo Controlled, Dose Ranging Study to Evaluate the Safety and Biological Efficacy of the Lipid-DNA Complex GR213487B in the Nasal Epithelium of Adult Patients with Cystic Fibrosis.* Sponsor: Glaxo Wellcome, Inc.

NIH/ORDA Receipt Date: 4-23-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

9705-187 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Hall, Simon J. and Woo, Savio L.C., Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral-Mediated Herpes Simplex Thymidine Kinase Gene Transduction in Conjunction with Ganciclovir Therapy as Neo-adjuvant Treatment for Patients with Clinically Localized (Stage T1c and T2b&c) Prostate Cancer Prior to Radical Prostatectomy.*

NIH/ORDA Receipt Date: 5-7-97. Sole FDA Review Recommended by NIH/ORDA: 5-28-97

9705-188 (Open) Gene Therapy/Phase I/Cancer/Chronic Myelogenous Leukemia/Chemoprotection/Tyr-22 Murine Dihydrofolate Reductase Gene/Antisense/Anti-b3a2BCR/ABL Gene/In Vitro/Autologous Peripheral Blood CD34+ Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Autologous Bone Marrow Transplant

Verfaillie, Catherine; McIvor, Scott; McCullough, Jeff;McGlave, Philip; University of Minnesota, Minneapolis, Minnesota; *Autologous Transplantation for Chronic Myelogenous Leukemia with Stem Cells Transduced with a Methotrexate Resistant DHFR and Anti-BCR/ABL Containing Vector and Post Transplant Methotrexate Administration.*

NIH/ORDA Receipt Date: 5-16-97. Sole FDA Review Recommended by NIH/ORDA: 6-6-97

9705-190 (Open) Gene Therapy/Phase I/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DOTMA-Cholesterol/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

O'Malley, Bert W., Johns Hopkins Medical Institutions, Baltimore, Maryland;*A Double-Blind, Placebo-Controlled, Single Rising-Dose Study of the Safety and Tolerability of Formulated hIL-2 Plasmid in Patients with Squamous Cell Carcinoma of the Head and Neck*. Sponsor: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 6-16-97

9706-191 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L., and Gleich, Lyon L., University of Cincinnati Medical Center, Cincinnati, Ohio; Swinehart, James M., Colorado Medical Research Center, Denver, Colorado; Hanna, Ehab, University of Arkansas for Medical Sciences/Arkansas Cancer Research Center, Little Rock, Arkansas; and Castro, Dan J.; University of California, Los Angeles, Los Angeles, California; *Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 6-6-97. Sole FDA Review Recommended by NIH/ORDA: 7-7-97

9706-194 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy/In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1 IIIB Envelope Protein/Intramuscular Injection

Aboulafia, David, Virginia Mason Clinic, Seattle, Washington; Campbell, Thomas, University of Colorado Health Sciences Center, Denver, Colorado; Kumar, Princy, Georgetown University Medical Center, Washington, D.C.; Murphy, Robert, Northwestern University Medical School, Chicago, Illinois; Skolnik, Paul, New England Medical Center, Boston, Massachusetts; Wheat, Joseph, Indiana University Hospital, Indianapolis, Indiana; *A Phase II, Randomized, Double Blind Placebo Controlled Study of Combination Drug Anti-Retroviral Therapy to Include a Reverse Transcriptase Inhibitor and a Protease Inhibitor Plus HIV-IT(V) or Placebo in HIV Patients with CD4+ Counts > 100, and HIV RNA > 1K, and < 10K.* Sponsor: Chiron Corporation.

NIH/ORDA Receipt Date: 6-23-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9706-196 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/gp91phox/Intravenous Infusion

Smith, Franklin O. and Dinauer, Mary C., Indiana University School of Medicine, Indianapolis, Indiana; *Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study.*

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 7-21-97

9707-200 (Open) Gene Therapy/Phase I/II/Cancer/Non-Hodgkin's B-Cell Lymphoma/Mantle Cell Lymphoma/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Intramuscular Injection

Levy, Ronald, Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 7-24-97. Sole FDA Review Recommended by NIH/ORDA: 8-13-97

9707-201 (Open) Gene Therapy/Phase I/ Cancer/Ovarian/Immunotherapy/In Vitro/Autologous Tumor Cells/Canarypox Virus/B7.1 (CD80)/Intraperitoneal Injection

Freedman, Ralph, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas; *Intraperitoneal (IP) Autologous Therapeutic Tumor Vaccine (AUT-OV-ALVAC-hB7.1) plus IP rIFN-g for Patients with Ovarian Cancer. A Pilot Study.* Sponsor: NIH NCI Cancer Therapy Evaluation Program.

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-202 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Melanoma/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Soiffer, Robert, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Melanoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-203 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Non-Small Cell Lung Carcinoma/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Salgia, Ravi, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Non-Small Cell Lung Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

IV. PROPOSED AMENDMENT TO APPENDIX M-I, *SUBMISSION REQUIREMENTS--HUMAN GENE TRANSFER EXPERIMENTS* , OF THE *NIH GUIDELINES*/MARKERT

Dr. Markert noted that the RAC recommended three modifications to the *NIH Guidelines* during the June 12-13, 1997, RAC meeting: (1) Eliminate the requirement for point-by-point responses to Appendices M-II through M-V; however, the questions raised in Appendices M-II through M-V must be addressed in the clinical protocol or as an appendix to the clinical protocol. She noted that the written comments submitted by Genzyme, Inc., disagreed with this recommendation. The disagreement appears to be a semantic issue of defining "clinical protocol." She suggested that the RAC should further clarify this language. (2) Modify the current requirement for submission of Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) approvals at the time of NIH/ORDA registration in accordance with Appendix M-I, *Submission Requirements-Human Gene Transfer Experiments*. The RAC recommended that investigators should not be required to submit IBC and IRB approval at the time of NIH/ORDA registration, but rather, submit evidence that the protocol has been submitted to the IBC for consideration. Submission of IBC and IRB approvals would not be required until after one of the following scenarios: (a) review by the full RAC, or (b) NIH/ORDA notification that the protocol is exempt from full RAC review. (3) Eliminate the requirement for submission of vector sequences to NIH/ORDA in accordance with Appendix I, *Submission Requirements - Human Gene Transfer Experiments*. Dr. Mickelson called on Dr. Markert to present the agenda item for RAC discussion.

IV-A. PROPOSED AMENDMENT TO APPENDIX M-I*, SUBMISSION REQUIREMENTS -- HUMAN GENE TRANSFER EXPERIMENTS* , OF THE *NIH GUIDELINES* REGARDING TIMING OF IBC AND IRB APPROVALS/ MARKERT

Dr. Markert noted that the language to eliminate prior IBC and IRB approvals from Appendix I, *Submission Requirements -- Human Gene Transfer* Experiments, is not clearly stated with regard to how RAC recommendations would be transmitted to the local IBC and IRB. Ms. Rothenberg was concerned about the scenario that RAC recommendation will be made prior to IRB review of the protocol and the Informed Consent document. Dr. Aguilar-Cordova recapitulated the RAC motion and stated that the intention of the motion is to allow IBCs an opportunity to receive and consider RAC concerns, if any, before the IBC grants final approval of the protocol; he noted that IRBs are not directly under the purview of the RAC.

Dr. Macklin inquired as to the reason that RAC recommendations will not be sent to IRB under the proposed amendments. Ms. Knorr explained that the proposed actions do not affect the RAC ability to forward its recommendations to the local IRB. The proposed actions currently stipulate that RAC recommendations, if any, will be forwarded to appropriate bodies including IRBs. These proposed actions only address the timing of submission of IBC and IRB approvals to NIH/ORDA.

Dr. Gordon stated that he favored RAC comments being forwarded to the IRB and IBC before final protocol approval is granted. Under this scenario, RAC comments will have greater impact on local oversight. Dr. Aguilar-Cordova agreed that in the face of relinquishing NIH approval of individual protocols, local IRB and IBC approvals should take RAC concerns into consideration.

Dr. Mickelson explained that IBCs generally grant conditional approval of human gene transfer protocols contingent on incorporation of any changes recommended by the RAC. Dr. Mickelson was concerned about the scenario in which protocols would be submitted to the RAC without local approvals. The local IBC and IRB should be the appropriate first bodies to review the protocol in detail.

Dr. Gordon restated his concern that the RAC should insist that final IBC and IRB approvals should be contingent on the RAC decision to exempt the protocol or upon receiving the RAC's recommendation regarding full review. Ms. Rothenberg said that if the local bodies choose to ignore RAC comments, they will have to be concerned with liability issues.

Ms. Rothenberg was concerned that if RAC reviews a protocol before IBC approval, the RAC will appear to micromanage the local authority. Dr. McIvor said that the RAC is not likely to micromanage local bodies since the RAC will review only novel protocols and most protocols are exempt from full RAC review. Dr. Lysaught noted that the RAC's comments would provide important advice to the local bodies. Dr. Markert said that the RAC will provide oversight to all human gene transfer protocols since the RAC will have a chance to prescreen the summary sheets of all the protocols submitted to NIH/ORDA. Dr. Juengst said that the RAC will review all aspects of the proposals including the Informed Consent document if the protocol is selected for full review.

Ms. Rothenberg stated that she would make a motion that before voting on the amendments to Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*, of the *NIH Guidelines*, the RAC should ask for a letter from the NIH Director to clarify NIH's position with regard to this issue of eliminating prior IBC and IRB approvals from the submission requirements. Dr. Juengst seconded the motion.

Ms. Rothenberg noted that prior local committee approvals are required as part of the NIH grant process. Ms. Knorr noted that historically when NIH has relinquished approval of certain categories of recombinant

DNA experiments considered as *Major Actions* under the *NIH Guidelines,* approval authority has been delegated to the local institution.

Dr. Markert stated that the RAC should pass a motion to delete prior IBC and IRB approvals from the submission requirement and forward the recommendation to the NIH Director for consideration. Dr. Gordon said that for novel protocols the local bodies should withhold their approval until after RAC discussion. Ms. Rothenberg stated that she would withdraw her motion to ask for a letter from the NIH Director. Dr. Greenblatt seconded the withdrawal of the motion.

Dr. Markert proposed to amend the proposed actions regarding Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*. The "Note" to the submission requirements is to be amended to read:

"Final IBC approval should be withheld until after: (1) NIH/ORDA notifies the IBC that the protocol is exempt from full RAC discussion, or (2) IBC receipt of RAC concerns and notification of whether the protocol has triggered full RAC review. Human gene transfer protocols shall not be initiated prior to submission of final IBC and IRB approvals to the NIH/ORDA."

Dr. Markert said that the intent of this amendment is to give local IBCs control of protocol approval, and that the IBC is expected to take RAC recommendations into consideration before granting final protocol approval.

Dr. Mickelson asked Dr. Markert to explain the item #2 in the amendment. Dr. Markert said that the intent is that IBC approval should be withheld until after notification by ORDA that the protocol has triggered full RAC review and the IBC has received the preliminary RAC comments. It is up to the IBC to decide if the protocol should be approved right away or if approval should be withheld until after full public review at the next RAC meeting.

Dr. Aguilar-Cordova stated that he would second Dr. Markert's motion. The motion would not place the RAC in the position of holding up a protocol approval longer than the IBC would wish to withhold approval. The local IBC possesses regulatory purview at the local level, and it can ignore RAC concerns if it chooses to approve the protocol before full RAC discussion.

Dr. Macklin inquired whether any minor concerns from the RAC will be forwarded to IBC if the protocol does not trigger full RAC review. Ms. Knorr explained that NIH/ORDA forwards all questions and concerns raised by the RAC to investigators. RAC members may take investigator responses into consideration before making a final decision regarding the necessity for full RAC review. Dr. Markert noted that her proposal would provide the IBC with the RAC feedback after reviewing the summary sheet. Drs. Macklin, Wolff, and Aguilar-Cordova agreed that the IBC should receive RAC concerns whether the protocol has triggered full RAC review.

Dr. McIvor clarified that the motions of the June 1997 RAC meeting do not include notifying IBCs with regard to RAC recommendations until after full RAC review of protocols. Dr. McIvor stated that before the RAC votes on this issue, the RAC should receive comments from individuals with IBC experience as to how receptive an IBC would be to withholding IBC approval until after full RAC review.

Dr. Greenblatt stated that from his experience, the IBC usually gives a provisional approval pending RAC review of human gene transfer studies. Dr. Mickelson said that the IBC could choose to wait for RAC feedback if they know that a protocol has triggered full RAC review. In the area of human gene transfer, some IBCs may not possess sufficient expertise and institutional memory to conduct an adequate review;

thus granting provisional approval contingent upon RAC review and subsequent recommendations.

Dr. Lai said that the spirit of Dr. Varmus' restructuring of the RAC is to delegate the protocol approval authority to the local level. The RAC should not try to recapture the authority that was lost in the restructuring.

Dr. Gordon stated that the process of full RAC review of novel protocols has placed the RAC in a difficult position if local IBCs decide to grant final approval of a novel protocol prior to RAC review. He speculated that any responsible local committee would hold its approval pending receipt of RAC comments. Dr. Lysaught said that the motion stated that the "Final IBC approval *should* (not must) be withheld until after: (1) NIH/ORDA notifies the IBC that the protocol is exempt from full RAC discussion, or (2) IBC receipt of RAC concerns and notification of whether the protocol has triggered full RAC review. Human gene transfer protocols shall not be initiated prior to submission of final IBC and IRB approvals to the NIH/ORDA." The IBC is urged, but not obligated, to withhold final approval of a protocol.

Dr. Macklin made a friendly amendment to the motion to include IRBs in addition to IBCs. She said that IRBs would equally benefit from RAC recommendations since they do not necessarily possess adequate expertise to review all aspects of a human gene transfer protocol. Dr. Juengst agreed that there is no reason to preclude the RAC from giving advice to IRBs. Dr. Lai suggested that the wording should be changed to add the additional first sentence, "IBCs and IRBs should be advised that a protocol is being reviewed by the full RAC...." Ms. Knorr stated that the investigators could be notified of any relevant RAC comments, and a copy of these comments could be forwarded to both the IRB and IBC. Dr. Markert agreed. Dr. Aguilar-Cordova seconded Dr. Macklin's friendly amendment to forward a copy of the RAC recommendations on a specific protocol to the IRB and IBC. Drs. Lysaught and Wolff said that both "IBC and IRB final approvals should be withheld until after: (1) NIH/ORDA notifies the IBC that the protocol is exempt from full RAC discussion, or (2) IBC receipt of RAC concerns and notification of whether the protocol has triggered full RAC review. Human gene transfer protocols shall not be initiated prior to submission of final IBC and IRB approvals to the NIH/ORDA."

Dr. Gordon was concerned that requiring IBCs and IRBs to withhold their final approvals until after RAC decision is contradictory to the spirit of relinquishing NIH approval. He said it would appear that the RAC is trying to recapture the approval authority. Ms. Rothenberg stated that the motion is not inconsistent with the spirit of restructuring the role of the RAC.

Dr. Ando stated that the spirit of the new RAC is to identify new issues rather than to approve individual protocols. Dr. Lysaught explained that the motion would provide advice to the IBC and IRB if the RAC flags a protocol for review.

Public Comments

Dr. Andrew Braun (Massachusetts General Hospital) stated that IBC authority is derived from the *NIH Guidelines*. If the RAC cedes its approval authority over human gene transfer protocols, so do the IBCs. This legal issue needs to be addressed. He noted that IBCs have been dealing with a variety of other biosafety issues in the absence of statutory authority. He noted that multicenter trials involve many different IBCs and IRBs; therefore, industry sponsors would face a situation where different stipulations arise from different local committees regarding a single multicenter trial. Dr. Braun suggested that the RAC table this issue until after the American Biological Safety Association has a chance to review and comment on this issue.

Ms. Rothenberg inquired what additional impact the motion would have on IBCs. Dr. Braun said that the

requirement to withhold approval would cause additional delay in the protocol approval process.

Dr. Joseph Rokovich (Pangaea Pharmaceuticals, Inc.) noted that without approval authority, the RAC still has a great deal of impact on human gene transfer protocols. With FDA notification to ORDA regarding IND submissions, the RAC will view all the protocols that have been proposed. Simple RAC discussion of protocols will have the attention of the protocol sponsors, the FDA representatives, and the public members in the audience because public communication has a tremendous power in absence of approval authority.

Mr. Steven Kradjian (Vical, Inc.) agreed with Dr. Rokovich about the power of RAC public persuasion. The RAC should provide the leadership role in area of policy and public influence rather than conducting individual protocol review. Public discussion of novel protocols is useful, and the approval issue is not that significant. Mr. Kradjian favored parallel review by IBC, IRB, FDA, and RAC without holding up protocol approval in a sequential manner.

Dr. Diane Fleming (Biosafety Consultant) suggested that RAC recommendations to IRB should be routed through the Office for Protection from Research Risks (OPRR). Dr. Fleming said that she has had extensive IBC experience with industry. Although industry is not obligated to abide by the *NIH Guidelines*, most sponsors choose to voluntarily observe the *NIH Guidelines* and value the cumulative wisdom of the RAC. She stated that preliminary IBC review of gene transfer protocols is essential.

Dr. Lysaught asked for Dr. Fleming's view on how the local IBC could best use the wisdom of the RAC on novel protocols such as *in utero* gene transfer or lentivirus applications. Dr. Fleming said that in the past, some IBC members may have accompanied investigators to the RAC meeting at which their protocol was being reviewed. IBCs will benefit from such a proposed RAC review. In terms of dealing with institutional biosafety issues, the IBCs need assistance from ORDA and the RAC. Convening a gene therapy conference with IBC representatives would be very useful.

Dr. Juengst stated that the RAC has a legitimate license to communicate with IRBs, because it already addresses IRB gene transfer issues in Appendix M. Ms. Rothenberg agreed. Dr. Macklin said that the motion should include transmittal of RAC recommendations to the IRB.

Dr. Lai made a friendly amendment to give IBCs and IRBs an option to decide whether they are going to accept the RAC's recommendations or not before granting final protocol approval. The IBC should be advised that a particular protocol is under separate review by the RAC, and that the final IBC approval should be withheld until after it is advised about RAC's concerns.

Ms. Knorr suggested that the RAC may consider several different options of the language that will be published in the *Federal Register* for public comments. The RAC may then vote on the options at the next RAC meeting.

Dr. Markert said that the first sentence that Dr. Lai proposed to add to her motion is not necessary; it already has addressed his concerns, i.e., IBC notification has already been included in the proposed language.

Dr. Aguilar-Cordova emphasized that the intent of the motion is to request that IBCs withhold final approval until after receiving and reviewing RAC's concerns. Dr. Lai agreed that the language should not convey the message that the RAC is trying to recapture approval authority. Dr. Aguilar-Cordova suggested starting the sentence, "The RAC recommends that final IBC and IRB approval be withheld until after NIH/ORDA provides...." Dr. Lai accepted the friendly amendment.

Option A

Dr. Mickelson called on Dr. Markert to restate her motion. Dr.Markert stated the motion as follows: "The RAC recommends that final IBC and IRB approvals be withheld until after NIH/ORDA provides IBC and IRB with RAC concerns (if any), and (1) NIH/ORDA notification that the protocol is exempt from full RAC review, or (2) NIH/ORDA notification that the protocol has triggered full RAC review. Human gene transfer protocols shall not be initiated prior to submission of final IBC and IRB approvals to NIH/ORDA."

Dr. Mickelson and Ms. Knorr noted that the investigators should be notified in addition to IBC and IRB. Dr. Markert agreed. Dr. Noguchi said that for rule-making purposes, the wording should be changed to the inclusive wordings, e.g., all appropriate persons or bodies as the notification parties, so that any additional parties may be added in the future without amending the *NIH Guidelines*. Dr. McIvor noted that if the purpose of the motion is to define the interaction between IBC,IRB, and the RAC, only those three parties should be mentioned in the motion.

Committee Motion 3 -- Option A

A motion was made by Dr. Markert and seconded by Dr. Aguilar-Cordova to modify the August 20, 1997, proposed actions regarding the "Note" to Appendix M-I, *Submission Requirements -Human Gene Transfer Experiments*, as follows:

"The RAC recommends that final IBC and IRB approvals be withheld until after NIH/ORDA provides IBC and IRB with RAC concerns (if any), and (1) NIH/ORDA notification that the protocol is exempt from full RAC review, or (2) NIH/ORDA notification that the protocol has triggered full RAC review. Human gene transfer protocols shall not be initiated prior to submission of final IBC and IRB approvals to NIH/ORDA."

The motion passed by a vote of 10 in favor, 0 opposed, and 2 abstentions.

This recommendation will be published in the *Federal Register* for public comment and voted on at the December 15-16, 1997, RAC meeting.

Option B

Dr. Ando proposed alternative language for the "Note" to Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*, as follows: "The RAC recommends that final IBC approval should consider: (1) NIH/ORDA notification of the IBC and/or the investigator of RAC recommendations, if any; (2) NIH/ORDA exempts the protocol from full RAC review; (3)NIH/ORDA notifies the investigator and/or IBC that the protocol has initiated full RAC review; (4) RAC recommendations, if any, after full RAC review; and (5) Notification of the IRB of RAC recommendations, if any." The motion was seconded by Dr. Juengst.

Dr. Aguilar-Cordova inquired about the impetus behind Option B as compared to Option A. Dr. Ando stated that the attempt is to address the concerns that the RAC has no direct purview over IRBs. The first four items are related to the primary RAC relationship to IBCs. As a secondary piece, the fifth item provides notification to IRB if there are any RAC concerns. Dr. Macklin indicated that the structure of the RAC relationship needs to be stated clearly. Dr. Lysaught noted that the tone of the wordings is softer in Option B than Option A, i.e., in Option B, "...final IBC approval should consider..., " instead of in Option A, "...final IBC and IRB approval be withheld..." Dr. Lysaught said that the wordings capture the spirit of RAC discussion, and she would volunteer to rewrite the proposal for RAC consideration later during in the

meeting.

Dr. McIvor stated that there is no need to propose alternative language to the Option A motion that the RAC has passed. Dr. Aguilar-Cordova suggested to table RAC voting on the proposal until later in the meeting.

IV-B. PROPOSED AMENDMENT TO APPENDIX M-I*, SUBMISSION REQUIREMENTS -- HUMAN GENE TRANSFER EXPERIMENTS* , OF THE *NIH GUIDELINES* REGARDING ELIMINATION OF THE REQUIREMENT FOR SUBMISSION OF APPENDIX M-I TO THE FDA/MILLER

In a letter dated November 20, 1996, Dr.Andra Miller, FDA, requested that the *NIH Guidelines* be amended regarding procedures for simultaneous submission of Appendix M materials to the RAC and FDA. The consensus of RAC discussion of this issue at the December 9, 1996, and March 6-7, 1997, RAC meetings was that the requirement for submission of Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments* of the *NIH Guidelines* to the FDA should be removed since the FDA does not accept responses to Appendix M in place of an IND application.

Other Comments

Dr. Lysaught inquired if the amendment would increase the number of incidents in which investigators fail to register Appendix M-I with NIH/ORDA. Ms. Knorr responded that the FDA indicated in its June 30, 1997, that it will notify NIH/ORDA of human gene transfer-related IND applications to ORDA. If any protocols are not submitted to ORDA, the investigators will be notified regarding ORDA submission requirements. Drs. Markert, Aguilar-Cordova, Gordon, and Lysaught agreed with the FDA request from Dr. Miller and stated that it is unnecessary to submit Appendix M-I material to the FDA.

Dr. Lysaught was concerned that without simultaneous submission, the RAC might receive the submission after IND approval by the FDA. Dr. Noguchi noted that the information provided by the FDA to ORDA regarding IND submissions will serve the purpose of identifying the investigators who are not in compliance with Appendix M-I. Dr. Noguchi said that the FDA will remind investigators of the necessity to register human gene transfer protocols with NIH/ORDA.

Committee Motion 3

A motion was made by Dr. Markert and seconded by Dr. Aguilar-Cordova to eliminate the requirement for submission of Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments* of the *NIH Guidelines* to the FDA. The motion passed by a vote of 12 in favor, 0 opposed, and no abstentions.

V. PROPOSED AMENDMENT TO SECTION III OF THE *NIH GUIDELINES* REGARDING APPROVAL REQUIREMENTS FOR THE PURCHASE AND USE OF TRANSGENIC RODENTS /AGUILAR-CORDOVA

Dr. Mickelson reminded the RAC of a letter dated September 10, 1997, from Dr. Joseph VanHouten, President of the American Biological Safety Association, to extend the public comment period by 60 days on the issue of transgenic rodents to allow sufficient time for the Association to consider this issue.

Section III-C-4, *Experiments Involving Whole Animals*, of the *NIH Guidelines* stipulates that all transgenic animal experiments are subject to IBC approval before initiation. In correspondence dated April 22, 1997, Dr. George Gutman, an IBC representative of the University of California, Irvine, California, inquired whether experiments involving the production or use of transgenic mice under Biosafety Level 1

containment could be initiated simultaneous with IBC notification. Current requirements under the *NIH Guidelines* require that IBC approval shall be obtained prior to initiation of such experiments. The RAC discussed this issue during its June 1997 meeting, recommending that this requirement should be changed to initiation simultaneous with IBC notification. The RAC agreed that the requirement of IBC approval prior to initiation is unnecessary and recommended that the *NIH Guidelines* should be amended such that: (1) the generation of transgenic rodents at the Biosafety Level 1 containment (not all animals) can be initiated simultaneous with IBC notification, and (2) the purchase and use of transgenic rodents should be exempt from the *NIH Guidelines*.

Dr. Aguilar-Cordova stated that the proposed amendments related to the use of transgenic rodents were a result of the RAC's deliberation of Dr. Gutman's inquiry at its June 1997 meeting. A motion was made to eliminate the requirement for prior IBC approval for the generation of transgenic rodents under Biosafety Level 1. In turn, generation of transgenic rodents under this level of containment could be initiated simultaneous with IBC notification. The RAC proposed that the purchase and use of such transgenic rodents, however, should be exempt from the *NIH Guidelines*. Under the existing *NIH Guidelines,* all experiments involving transgenic rodents require IBC approval prior to initiation. The RAC agreed with Dr. Gutman that the increasing use of transgenic animals was placing an unnecessary burden on IBCs. Dr. Aguilar-Cordova noted that the amendments are more consistent with prevalent laboratory practice.

Dr. Mickelson stated that the language needs to be clarified regarding the statement, "the purchase and use of transgenic rodents should be exempt from the *NIH Guidelines."* Dr. Gordon noted the existence of the *NIH Guidelines on the Care and Use of Animals*. The use of transgenic rodents should not be exempt from the *NIH Guidelines*, because the use is covered by the other NIH guidance document. Dr. Gordon stated that purchasing an animal that is produced under scrutiny may be exempt from the *NIH Guidelines.* He suggested deleting the two words, "and use," from the language of the amendment. Dr. Mickelson agreed.

Dr. Aguilar-Cordova made a motion to accept the proposed action by deleting two words, "and use" from the statement, "... (2) The purchase of transgenic rodents should be exempt from the *NIH Guidelines*." Dr. Greenblatt seconded the motion.

Committee Motion 4

A motion was made by Dr. Aguilar-Cordova and seconded by Dr. Greenblatt to modify the August 20, 1997, proposed actions, and to accept the amendments to the *NIH Guidelines* with regard to: (1) the generation of transgenic rodents at the Biosafety Level 1 containment (not all animals) can be initiated simultaneously with IBC notification, and (2) the purchase of transgenic rodents should be exempt from the *NIH Guidelines*. The motion passed by a vote of 11 in favor, 0 opposed, and no abstentions.

This recommendation will be published in the *Federal Register* for public comment and voted on at the December 15-16, 1997, RAC meeting.

VI. PROPOSED AMENDMENT TO THE APPENDIX M-I, *SUBMISSION REQUIREMENTS -- HUMAN GENE TRANSFER EXPERIMENTS* , OF THE *NIH GUIDELINES* REGARDING ELIMINATION OF THE REQUIREMENT FOR POINT-BY-POINT RESPONSES TO APPENDICES M-II THROUGH M-V

The RAC revisited the issue of eliminating the point-by-point responses to Appendix M-II through M-V, in response to the September 8, 1997, letter from Dr. Alex Kuta, Genzyme Corporation. Genzyme disagreed with the proposed action to incorporate the responses to Appendix M-II through M-V into the clinical protocol.

Dr. McIvor stated that the current proposed actions specify that the following information should be submitted to NIH/ORDA in accordance with Appendix M-I, *Submission Requirements --Human Gene Transfer* Experiments: (1) scientific abstract, (2) non-technical abstract, (3) clinical protocol (including discussion of all issues raised in Appendix M-II through M-V), (4) Informed Consent document prepared for IRB submission, (5) letter stating that submission has been made to the IBC, (6) appendices (including tables, figures, and manuscripts), and (7) curricula vitae for each key professional person in biographical sketch format.

Dr. McIvor made a motion to revise this language such that responses to the questions raised in Appendices M-II though M-V must be provided either in the clinical protocol or as an appendix to the clinical protocol. The amendment would allow more flexibility for investigators on how to prepare the submission material.

Dr. Lysaught noted that the proposed revised version does not completely addressGenzyme's concern about the requirement to include all responses to Appendix M-II through M-V.

Dr. Aguilar-Cordova seconded the motion, and he made a friendly amendment to the proposed language to read, "Discussion of all pertinent issues raised in Appendix M-II through M-V...." He noted that not all questions raised in Appendix M-II through M-V are pertinent to all protocols, e.g., protocols using retroviruses vs. adenoviruses. Dr. McIvor accepted the friendly amendment.

Dr. Gordon was concerned about the meaning of the word, "pertinent." The investigators may choose thei own interpretation and not respond to all questions. Dr. Aguilar-Cordova said that the intention is to make it simple for the investigators. Dr. Markert agreed that "pertinent" is a proper word for the statement.

Ms. Sheryl Osborne (NeuroVir, Inc.) stated thatGenzyme's concern may focus on the inclusion of proprietary information in the clinical protocol

Dr. McIvor explained that the issue of proprietary information is separate from the issue of point-by-point responses to Appendix M. Genzyme's concerns relate to the necessity of preparing of a separate document if those issues are already discussed within the context of the clinical protocol.

Ms. Rothenberg noted one of industry's major concerns appears to be the issue of proprietary information. Dr. McIvor inquired how NIH/ORDA handles proprietary information. Ms. Knorr explained that at present there is very little information submitted toORDA that is marked as confidential. Ms. Knorr noted that ORDA is a public office, and the RAC's a public advisory committee. The investigators and sponsors submitting any information to NIH/ORDA should not be designated as "confidential" in its entirety. In the event that an investigator or sponsor determines that specific responses to one or more of the items described in Appendix M should be considered as proprietary or trade secret, each item should be clearly identified as such. The cover letter (attached to the submitted material) shall: (1) clearly indicate that select portions of the application contain information considered as proprietary or trade secret, (2) a brief explanation as to the reason that each of these items is determined proprietary or trade secret. Ms. Rothenberg was satisfied with the response.

Dr. Lysaught was still concerned about the subjective interpretation of the word, "pertinent." Most questions raised in Appendices M-II through M-V are pertinent to the RAC. Dr.Markert said that choosing the word, "pertinent," would give investigators the flexibility to respond to the questions as they deem appropriate. Additional information may be requested by the RAC during further review.

Ms. Victoria Allgood (Gene Medicine, Inc.) suggested using the words, "directly applicable" rather than "pertinent." Most of the Appendix M questions are pertinent, but not all questions are directly applicable to all protocols, e.g., non-viral vectors used mostly by her company.

Drs. Markert and McIvor noted that most questions regarding this amendment have been discussed by the RAC.

Committee Motion 5

A motion was made by Dr. McIvor and seconded by Dr. Aguilar-Cordova to eliminate the point-by-point responses to Appendix M-II through M-V. Discussion of all pertinent issues raised in Appendix M-II through M-V must be provided either in the clinical protocol or as an appendix to the clinical protocol. The motion passed by a vote of 10 in favor, 2 opposed, and no abstentions.

VII. DISCUSSION REGARDING THE FIRST GENE THERAPY POLICY CONFERENCE (GTPC) ENTITLED: *HUMAN GENE TRANSFER - BEYOND LIFE-THREATENING DISEASE* /MICKELSON, JUENGST, AND ROTHENBERG

GTPC Report

Dr. Juengst reported to the RAC on the first Gene Therapy Policy Conference (GTPC) entitled: *Human Gene Transfer - Beyond Life-Threatening Disease* held on September 11, 1997, at the Bethesda Holiday Inn, Bethesda, Maryland. The GTPC was sponsored by ORDA. The co-chairs were Drs. Mickelson and Juengst.

The GTPC covered three major topics. (1) Scientific Prospects For Enhancement Through Gene Transfer The speakers were: Theodore Friedmann, Ph.D., University of California San Diego, La Jolla, California; Hunt Willard, Ph.D., Case Western Reserve University, Cleveland, Ohio; and W. French Anderson, M.D., University of Southern California, Los Angeles, California. (2) The Treatment/Enhancement Distinction: Conceptual, Ethical, and Social Issues. The speakers were: Eric Juengst, Ph.D., Case Western Reserve University, Cleveland, Ohio; Thomas H. Murray, Ph.D., Case Western Reserve University, Cleveland, Ohio; and Sheila M. Rothman, Ph.D., Columbia University, New York, New York. (3) Development of a "Treatment/Enhancement" Distinction as Part of a Guidance Document. The speakers were: Anita Silvers, Ph.D., San Francisco State University, San Francisco, California; Maxwell Mehlman, Ph.D., Case Western Reserve University, Cleveland, Ohio; and Claudia Mickelson, Ph.D., Massachusetts Institute of Technology, Cambridge, Massachusetts.

Dr. Juengst noted the issues and questions raised by panelists were as follows:

1. The RAC should focus its efforts on public education of gene therapy issues. When doing so, the RAC should acknowledge that it is not yet known whether technologies to alter human nature will be determined or not;

2. Gene enhancement is "going to happen quickly". Such proposals will most likely be submitted under the guise of medical therapies; however, it will be the "off label" uses of these applications and the implications of such a trend that the RAC should consider. The RAC and the FDA must be prepared for the likely submission of gene enhancement protocols by preparing guidelines on how to identify potential "enhancement" uses.

3. The RAC should review the *Points to Consider* to determine whether some additional issues should be

included regarding submittal of protocols for gene enhancement interventions;

4. The RAC should discuss whether it would entertain a mock protocol for gene enhancement as was submitted by Dr. W. French Anderson for the first human gene therapy protocol. Dr. Anderson stated that he did not endorse RAC's consideration of a mock gene enhancement protocol; society has not been adequately educated as to the potential risks and benefits involved in genetic enhancement research and application.

5. A clear distinction needs to be made between gene therapy and gene enhancement protocols. Such a distinction will be especially important for consideration of third party payments; if the intervention is not medicalized, it should not be covered by insurance.

Dr. Juengst noted that the panelists reached consensus on the following points:

1. The RAC should make public education and moral leadership regarding gene enhancement its primary mission by promoting discussion of important issues and disseminating information, e.g., preparing a paper that presents the benefits and risks of gene enhancement.

2. The NIH Director should assume a leadership role by endorsing research and treatment of orphan diseases (e.g., supporting basic research on gene regulation).

3. The RAC should revisit the *Points to Consider* to determine whether language should be inserted with regard to its position on genetic enhancement.

Dr. Mickelson stated that the RAC's role and responsibilities should include the following:

1. Clarifying the differences between gene therapy and gene enhancement; Giving advice on resource allocation;

2. Holding additional policy conferences on such issues as *in utero* gene therapy, germ line gene therapy, DNA vaccines, and new vectors; and

3. Assessing the scientific, ethical, and social merit of proposed areas of human gene transfer research and protocol development.

Ms. Rothenberg noted that the draft of the *Conference Highlights* needs to be verified against the transcript of the conference to ensure accuracy of the record.

Dr. Markert was concerned about the recommendation that the RAC's role includes giving advice to the NIH Director on resource allocation.

Dr. Mickelson suggested that a representative from OPRR should be included as a non-voting member of the RAC to provide more understanding of its oversight responsibilities in relation to IRBs. It is very helpful in resolving the issues of gene transfer protocols by having Dr. Noguchi from the FDA participate in the RAC meetings as a non-voting member of the RAC.

Ms. Rothenberg made a motion to invite a representative from OPRR as a non-voting member of the RAC. Dr. Macklin seconded the motion.

Dr. Greenblatt stated that he is in favor of this proposal, because it will improve communication between the RAC and IRBs.

Committee Motion 6

A motion was made by Ms. Rothenberg and seconded by Dr. Macklin to invite a representative from the Office for Protection from Research Risks as a non-voting member of the RAC. The motion passed by a vote of 11 in favor, 0 opposed, and no abstentions.

Germ-Line Intervention Forum

Dr. Mickelson noted that there is a meeting entitled: *Forum on Human Germ-Line Intervention*, to be held on September 24-25, 1997, in Washington, D.C. The *Forum* is sponsored by the American Association for the Advancement of Science, The Program of Dialogue Between Science and Religion and the Scientific Freedom, Responsibility, and Law Program. Several members of the RAC and panelists of the GTPC will be attending the *Forum*.

VIII. FUTURE GTPC TOPICS

Dr. Mickelson suggested convening the second GTPC in conjunction with the March 1998 RAC meeting, and she called on the RAC to suggest possible topics of importance.

Dr. Aguilar-Cordova suggested that the March 1998 GTPC should focus on herpesvirus vectors and/or lentivirus vectors; protocol submissions using these new vectors are imminent.

Dr. Gordon acknowledged the need for discussion of new vectors; however, there is an urgency to address the limitations and risk versus benefit of novel gene transfer approaches, e.g., *in utero* gene transfer and germ-line intervention. Most of the topics discussed at the September 1997 GTPC use the existing somatic gene transfer procedures for diseases, and the distinction between the therapeutic and enhancement applications are not great.

Ms. Rothenberg noted that the GTPC on gene enhancement was a timely topic on the eve of the release of the new movie entitled: *"GATTACA."* Public education about realistic expectations about gene enhancement intervention is timely.

Dr. Lysaught pointed out the need for different formats to deal with ethical issues such as gene enhancement intervention versus scientific issues of new vectors and new gene transfer approaches. The former are issues less well defined and require many visits to the same topic in order to arrive at a useful conclusion.

Dr. McIvor stated his preference that the March 1998 GTPC should focus on broader issues such as *in utero* and germ-line gene intervention; however, the RAC could invite experts to the December 1997 meeting for the purpose of educating members of the committee and the public about issues related to novel gene delivery vectors, e.g., lentiviruses and herpesviruses. The RAC needs to be fully informed about these new vectors before it actually receives such protocol submissions.

Dr. Markert stated that it would be very valuable to the RAC to have two panels of experts to deal with lentivirus and herpesvirus vectors. Issues surrounding the ramification, safety, risks, potential, and public perception are very pertinent to the RAC when it reviews the protocol submissions.

Dr. Ando stated that rapid advances are being made in the development of both lentivirus and herpesvirus vectors, but the RAC may not see these protocols until their development is far advanced since IRB and IBC approvals are required for their submission to ORDA under the current *NIH Guidelines*. He suggested that discussion of mock protocols based on the animal models would be very useful.

Dr. Macklin noted two important ways for the RAC to decide critical discussion issues: (1) Anticipate areas of gene transfer research that might arouse serious public concern once scientific advances are made known to the public. The sheep cloning experiment is an example of such an issue. (2) Conduct outreach surveys to determine the issues that of most concern to the general public.

Dr. Aguilar-Cordova made a motion to convene the March 1998 GTPC on lentivirus vectors; he asked Dr. Ando if he would be willing to develop a "mock" lentivirus protocol to be used as the basis for RAC discussion. Dr. Aguilar-Cordova noted that the public perception of lentiviruses that include HIV may be more alarming than herpesviruses. As for herpesvirus vectors, Dr. Aguilar-Cordova suggested that *ad hoc* experts could be invited to address the RAC at its December 1997 meeting. Dr. Juengst seconded the motion.

Dr. Juengst that GTPC topics should be alternated between the broader societal issues to engage public discussion and the narrower scientific issues such novel vectors, which are of immediate concern to the gene therapy community. He suggested broadening the December RAC discussion to include new technologies other than the lentivirus and herpesvirus vectors.

Dr. Noguchi suggested that the RAC consider *in utero* gene transfer at its next GTPC. Dr. Noguchi noted that from FDA's perspective, these protocols are imminent; and that the FDA needs feedback from RAC's public forum to address these issues. *In utero* gene transfer with murine retrovirus vectors or lentivirus vectors are both very pertinent. It is useful to consider a "mock" protocol for *in utero* lentiviral gene transfer.

Dr. Gordon suggested that instead of convening a GTPC on these new technologies, the RAC may consider inviting experts in these areas to give a series of seminars at the next RAC meeting. The experts may provide an overview of new vectors based on herpesviruses and lentiviruses, and address the issues of basic biology, potential, limitation, and danger of these new vectors for human gene transfer.

Ms. Rothenberg noted that Dr. Gordon's suggestion of seminars and GTPCs are not mutually exclusive. She suggested that at the December 1997 RAC meeting, the RAC should invite seminar speakers to address these topics. The GTPC may be convened in conjunction with the March 1998 RAC meeting to develop gene therapy policy.

Dr. Noguchi agreed that regulatory policy on these new vectors and on *in utero* gene transfer is very urgent. He foresees that protocols will be submitted in the very near future. He suggested that a GTPC on these issues is important.

Dr. Aguilar-Cordova amended his motion to include discussion of a "mock" protocol involving lentivirus vectors and *in utero* gene therapy at the March 1998 GTPC. Expert speakers should be invited to give seminars at the December 1997 RAC meeting. Ms. Knorr noted that Dr. Varmus will consider the RAC recommendations for a March 1998 GTPC topic; however, the final decision will be made by the NIH Director. Any issue not covered by a GTPC can be accommodated during a regularly scheduled RAC meeting. Dr. Juengst accepted the friendly amendment.

Dr. Juengst noted that the ethical and policy issues surrounding *in utero* gene transfer are integral parts of

the scientist's concerns. Dr. Ando agreed that the impact of lentiviruses involves scientific, legal, ethical, and social issues.

Dr. Gordon suggested having a flexible format for the March 1998 GTPC. In the meantime, the RAC should have seminars from experts on lentivirus, herpesvirus, and other new technologies since protocols may be submitted before the March 1998 RAC meeting. Dr. Markert agreed with Dr. Gordon, and Dr. Aguilar-Cordova accepted the friendly amendment.

Committee Motion 7

A motion was made by Dr. Aguilar-Cordova and seconded by Dr. Juengst to recommend to the NIH Director that the topic of the March 1998 Gene Therapy Policy Conference be on the lentivirus vectors and *in utero* gene therapy, e.g., a "mock" gene transfer protocol. The RAC should invite experts as seminar speakers regarding herpesvirus and lentivirus vectors at the December 1997 RAC meeting. The motion passed by a vote of 11 in favor, 0 opposed, and no abstentions.

Other Comments

Dr. Lysaught inquired about a letter dated August 13, 1997, from Dr. Russell J. Howard of Maxygen (Santa Clara, California) requesting RAC discussion of "gene shuffling" technology. Ms. Knorr noted that most RAC members favored such a discussion and recommended soliciting comments from industries regarding new technologies worthy of RAC discussion.

Dr. Mickelson asked RAC members to forward to her, Dr. Juengst, or ORDA their comments and recommendations regarding the *1st GTPC Conference Highlights on the Human Gene Transfer: Beyond Life-Threatening Disease*. Dr. Juengst agreed to assist in the preparation of the final report to the NIH Director on the GTPC. Ms. Knorr noted that an executive summary of the GTPC is needed as a report to the public.

IX. CONTINUED DISCUSSION OF PROPOSED AMENDMENTS TO APPENDIX M-I, *SUBMISSION REQUIREMENTS -- HUMAN GENE TRANSFER EXPERIMENTS*, OF THE *NIH GUIDELINES* REGARDING TIMING OF IBC AND IRB APPROVALS/MARKERT

Option B

Dr. Ando proposed Option B as the alternative language for the "Note" to Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*. It was briefly discussed by the RAC in a previous session and was tabled for further discussion. Option B reads as follows:

"The RAC recommends that final IBC approval should consider: (1) NIH/ORDA notification of the IBC and/or the investigator of RAC recommendations, if any; (2) NIH/ORDA exempts the protocol from full RAC review; (3) NIH/ORDA notifies the investigator and/or IBC that the protocol has initiated full RAC review; (4) RAC recommendations, if any, after full RAC review; and (5) Notification of the IRB of RAC recommendations, if any."

The motion was seconded by Dr. Juengst.

Dr. Mickelson stated that the Option B is intended as alternative language to be published in the *Federal Register* for public comment. Dr. Lai noted that the language of Option B is very similar to Option A which the RAC already accepted. Ms. Rothenberg stated that the RAC should choose one of the two options;

otherwise, the public will be confused. Dr. Ando suggested that the RAC should vote to accept or reject the alternative language. Dr. Lysaught noted that the Option B does not use the language to require withholding IBC/IRB approvals until the RAC makes its recommendation. It is a softer version of the statement, and it distinguishes different levels of conveying RAC concerns to IBC and IRB. Dr. McIvor called the vote on Option B.

Committee Motion 8

A motion was made by Dr. Ando and seconded by Dr. Juengst to propose an alternative language to be published in the *Federal Register* as Option B for the "Note" to Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*. The Option B states:

"The RAC recommends that final IBC approval should consider: (1) NIH/ORDA notification of the IBC and/or the investigator of RAC recommendations, if any; (2) NIH/ORDA exempts the protocol from full RAC review; (3) NIH/ORDA notifies the investigator and/or IBC that the protocol has initiated full RAC review; (4) RAC recommendations, if any, after full RAC review; and (5) Notification of the IRB of RAC recommendations, if any."

The motion failed by a vote of 3 in favor, 7 opposed, and 2 abstentions.

X. DISCUSSION OF AMENDMENT TO HUMAN GENE TRANSFER PROTOCOL #9701-171 ENTITLED: *IMMUNE RESPONSE TO INTRADERMAL ADMINISTRATION OF AN ADENOVIRUS 5 GENE TRANSFER (AD $_{GV}$CD.10) IN NORMAL INDIVIDUALS* PIs: Ben-Gary Harvey and Ronald Crystal, Rockefeller University
Summary: Mickelson

Presentation--Dr. Crystal

In a letter dated August 28, 1997, Dr. Crystal proposed an amendment to Protocol #9701-171, entitled: *Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector (AD$_{GV}$CD.10) in Normal Individuals.* In his letter, Dr. Crystal stated that based on the knowledge that administration of the Ad$_{GV}$CD.10 vector to normal subjects elicits local inflammation and systemic neutralizing anti-adenoviral immunity, this amendment seeks to determine if oral corticosteroids will suppress this immune response. This hypothesis is based on studies in immunocompetent experimental animals showing that a variety of immunosuppressants, including corticosteroids, will suppress host responses induced by adenovirus vectors.

Dr. Crystal gave a slide presentation explaining the proposed amendment. As a point of clarification, he stated that the proposed amendment to use corticosteroids is not prompted by any adverse effects of the vector; instead the purpose is to determine if corticosteroids will dampen the immune response.

Dr. Crystal stated that the purpose of using normal subjects is to evaluate the host immune responses to adenoviral vectors. Such information is unavailable by studying subjects with diseases or in animal models. The protocol that is the subject of this amendment involves intradermal administration of an adenoviral vector to normal subjects. (It should be noted that Dr. Crystal has submitted a second protocol using normal subjects to evaluate the host immune response that results from intrabronchial administration of an adenoviral vector to the lung.) The vector expresses the cytosine deaminase gene and is the same vector used in the colon cancer protocol (#9509-125). The concept is to evaluate immunity against adenovirus as a function of time in the lung epithelial lining. Animal experiments have

been performed in rats in which gene expression has been detected as a function of time when the vector is administered to the animals for the first time. No such expression is observed if a repeat administration is performed several weeks later. High levels of neutralizing antibodies have been detected which inhibit the sustained gene expression necessary for successful gene therapy in cystic fibrosis (CF) patients. In humans, the reaction to the vector is different from the rat. In one CF patient, no neutralizing antibody was observed after several repeat administrations to the lung. Dr. Crystal emphasized that mice are not humans and that is the rationale used to propose studies on normal subjects.

Dr. Crystal said that the study is conducted in normal patients because the risk is low. In CF patients, the lung is filled with pus. In CF lung lavage, the epithelial fluid is purulent, and it cannot be used to assess immunoglobulins. 40% of cystic fibrosis patients will develop fevers following bronchial alveolar lavage, and the risk is high. In normal lung lavage, one can assess humoral and cellular immunity. Less than 5% of normal subjects are expected to develop fevers; therefore, the risk is considerably lower.

Dr. Crystal said intrabronchial vector administration is safe, because the vector is administered to a very localized area of the lung. The vector will be administered by a spray from the bronchoscope to a 3 centimeter area. This strategy of vector administration has been performed on 14 CF patients with 35 administrations of a similar vector with the cystic fibrosis transmembrane conductance regulator (CFTR) transgene ranging from doses of 10^6 to 10^9 plaque forming units (pfu) over a period of 6 months. He said that 2 patients received 3 x $10^{8.5}$ pfu every 2 weeks for a total of 4 administrations with no observable adverse effects. A total of 148 bronchoscopic procedures have been performed on 16 patients with no adverse events.

Dr. Crystal explained that inclusion of corticosteroids is designed to test the hypothesis that immunosuppression will reduce host responses to the adenovirus. The hypothesis will be tested first with corticosteroids as immunosuppressive drugs in the intradermal protocol. Other immunosuppresives to be tested in the future include cyclosporin, FK506, cyclophosphamide, and methotrexate. Corticosteroids have been used several times in CF patients with no adverse effects. Corticosteroids have been used in normal subjects outside the adenovirus gene transfer context at doses higher than those proposed for this study. This dose is absolutely safe. The present amendment is intended to explore the biology of immunosuppresive agents in extending the duration of transgene expression and in reducing immune reactions to the adenovirus vector.

Other Comments

Dr. Lai noted that there are no neutralizing antibodies in the blood of CF patients after adenovirus administration to the lung. He asked if this phenomenon is due to lack of lymphocytes in the epithelial lining fluid. Dr. Crystal responded that the number of lymphocytes in the lavage fluid of the CF patients is less than that seen in normal individuals, but it is uncertain if the number is related to long-term gene expression. In CF patients, the fluid is full of neutrophils that hampered evaluation of the study, but he expects that using normal subjects will resolve this issue.

Dr. Lai asked if the present adenovirus vector offers promising benefits for CF patients. Dr. Crystal responded that he can achieve normal transgene expression for a short period of 1 week, but 30 days after vector administration the transgene is no longer expressed. It is hoped that the presence of corticosteroids will prolong the duration of transgene expression.

Dr. Aguilar-Cordova posed two questions on behalf of Dr. Wolff who left earlier: (1) How would the results obtained from the proposed amendment influence the design of future protocols with therapeutic endpoints? (2) Because E1-deficient adenoviruses can replicate in human cells under certain conditions,

how would this data impact on the protocol? In addition, Dr. Aguilar-Cordova inquired if the CF patients are more vulnerable to immunosuppression than normal individuals. As a point of clarification, Dr. Crystal said that the amendment proposes using corticosteroids for normal individuals rather than for CF patients. With regard to the question of vector replication, Dr. Crystal stated that adenovirus vector replication neve has been observed in any human gene transfer trials. (It should be noted that the RAC has determined that the level of detection for replication competent virus for adenoviral protocols is 1 in 10^9.) It is observed only in certain human cell lines *in vitro*. To address the first question on future studies, Dr. Crystal emphasized the vital importance of the data obtained from normal subjects concerning the basic biology of the vector. The data will provide the rationale for the design of future generations of adenovirus vectors and clinical protocols.

Dr. Markert found Dr. Crystal's study interesting. She asked if the proposed corticosteroid dosage is large enough to see any effect on the immune response. Dr. Crystal responded that the reason the low dosage was chosen is because it is below the safe dosage for normal subjects, and it would be the maximum dosage to be used in CF patients. Dr. Crystal said that the proposed dose has pharmacologic effects, i.e., lowering the lymphocyte counts within 2 hours, suppressing skin reactions, and suppressing lymphocyte proliferative responses. The purpose of the study is to determine if corticosteroids are effective for adenovirus vector administration.

Dr. McIvor asked two questions: (1) Has the systemic cell-mediated immune response been studied in CF patients? (2) What is the relevance of cytosine deaminase gene expression to the use of the adenovirus vector expressing the CFTR gene in the lung of CF patients? Dr. Crystal responded that safety is the reason for choosing the heterologous cytosine deaminase gene rather than the autologous CFTR gene for the normal subjects because the latter has an autoimmune concern. Dr. Crystal said that he has not observed any systemic cell-mediated immune response to the vector in CF protocols.

Dr. Gordon inquired how Dr. Crystal envisions that corticosteroids would be effective for the CF patients if they do not have any systemic humoral and cellular immune response to the vector. Dr. Crystal said that the key issue is the local immune responses in the lung rather than the systemic responses. CF patients are not suitable to study the local reactions, that is the reason to choose the normal subjects.

Dr. Aguilar-Cordova inquired about the corticosteroid amendment. Dr. Crystal responded that the amendment is to add an additional arm to the intradermal protocol by including corticosteroids in the study; all other aspects of the protocol remain unchanged. Corticosteroids will not be used for the proposed lung administration in normal subjects. Dr. Aguilar-Cordova asked how the intradermal study would benefit the proposed lung protocol. Dr. Crystal said that intradermal administration is a safer route to begin this series of studies in normal subjects, however, the normal lung study has a more direct relevance to clinical medicine, such as CF. Dr. Aguilar-Cordova asked if Dr. Crystal implied that intrabronchial lung administration is risky. Dr. Crystal responded no. Dr. Aguilar-Cordova asked how intradermal dosage would be related to the intrabronchial dosage. Dr. Crystal said that the maximum intradermal dose is lower than that of the intrabronchial dose due to the volume limitation of the vector to be administered to the skin. Dr. Crystal explained that the intradermal protocol is just a safer protocol to lead off this series of studies. It is a rational approach to push the envelope of performing gene transfer on normal subjects by choosing to begin with a safer approach.

Dr. Markert stated that she is sympathetic to Dr. Crystal's choice of starting the studies with the intradermal route. She asked if the major immune problem in the lung is due to T-cell mediated response. Dr. Crystal responded that his hypothesis is that both the humoral and cell-mediated immune responses are important factors for successful lung administration.

Dr. Lai inquired if the data obtained from theintradermal injection is directly applicable to the intrabronchial study. Dr. Crystal responded that definitive information can only be obtained from the target organ of vector administration, i.e., the lung. The choice ofintradermal injection is primarily for safety concerns. In addition, valuable biologic information will be obtained that will provide an interesting paradigm for future study of adenovirus vectors andtransgene expression. Dr. Crystal said that the information will be useful in terms of developing vaccines using adenoviruses.

Dr. Lai asked if the present adenovirus construct proves to be unsatisfactory for the treatment of CF, could any useful information be obtained by studying this construct in normal subjects? Dr. Crystal noted that successful transgene expression within the first week of vector administration has been obtained with this "first generation" vector in CF patients. He hypothesized that in combination with corticosteroids, the duration of transgene expression will be prolonged.

Dr. Markert inquired if Dr. Crystal has observed any immune responses in the lung in individuals receiv intradermal injections of the vector. She asked whether the corticosteroid effects can be detected if th response is low. Dr. Crystal responded that he has observed remarkable neutralizing antibodies in the lung in addition to the expected cellular response. He noted that although the cellular immune response is mild, the low level response still will be useful to detect any different effects between plus and minus corticosteroids experiments proposed in the amendment.

Dr. Aguilar-Cordova inquired if the levels of neutralizing antibodies subside over a period of time. Dr. Crystal said that the level peaked 2 weeks following vector administration; levels returned to normal by approximately 60 days. Dr. Crystal noted that such a neutralizing antibody rise was not observed in the blood of the CF patients. In normal individuals, both blood and lung levels are elevated after intradermal administration. Dr. Crystal said that he would expect to see a similar antibody response in normal individuals when the vector is administered to the lung. Dr. Aguilar-Cordova asked why CF patients do not have antibodies in the blood. Dr. Crystal said the study is to seek some explanation for this observation.

Dr. Lai still expressed concern about using first generation adenovirus vectors for intrabronchial administration. The procedure is invasive considering the limitation of these vectors. Dr. Crystal stated that it is a waste of resources to perform the study with second and third generation vectors without having proper information about the basic biology of the first generation vector.

Dr. Lysaught inquired if corticosteroids have been used in CF patients. Dr. Crystal noted that originally corticosteroid usage is an exclusion criterion for entering onto the CF protocols. Due to difficulty in finding suitable CF patients, the FDA has granted permission to enroll a couple of CF patients on steroid treatment. Dr. Lysaught asked if persistence of transgene expression has been observed in th patients. Dr. Crystal responded that he cannot provide a definitive answer to this question, because the CF study is a dose escalation study and the steroid patients are those in the highest dose cohort of 10^9 pfu . The duration of gene expression varies with the dose. The higher the vector dose, the stronger th immune response and the shorter the duration of gene expression.

Dr. Gordon inquired how CFTR expression is evaluated in the CF patients. Dr. Crystal said th vector-driven CFTR messenger ribonucleic acid (mRNA) is compared with the endogenous mRNA leve by a quantitative polymerase chain reaction (PCR) assa

Dr. McIvor asked if any symptoms were ameliorated in the CF patients receiving the CFTR adenovirus their lung. Dr. Crystal explained that the vector has been administered to a 3 cm local area and it is not expected to have any symptomatic effect. In addition, Dr. Crystal stated that expression of CFTR mRN

levels in this 3 cm local area are at least 5 % of the level observed in non-CF individuals. Wild type CFTR mRNA levels of 5 % or greater are accepted in the field as probably being curative. And therefore, Dr. Crystal indicated that he can cure CF. Dr. McIvor cautioned that one should not make any public statement of any curative effect of CF gene therapy. Dr. Crystal further clarified that he can correct the biological expression of CFTR in a defined, 3 cm, area of the lung. Dr. McIvor asked if CFTR g expression is observed in the intended target cell population. Dr. Crystal said that such definitive data are not yet available. Gene therapy has a long way to advance to a cure for CF patients.

Dr. Gordon asked how the protocol will be evaluated to observe if the CFTR gene is expressed in prop target cells. Dr. Crystal said that bronchoscopy will sample cells in the area administered with the vecto and that glandular or epithelial cells will be studied to determine if there is any CFTR expressio

Dr. Noguchi noted that Dr. Crystal's amendment is to evaluate if corticosteroids might suppress the undesirable immune response to the adenovirus vector via intradermal injections. Many times potentia valuable drugs in development are discarded prematurely before moving on to testingthe second or thi generation products. The data regarding the basic vector biology is valuable for the future development of the vector. At this point, it is unclear whether the second or third generation vectors would offer any advantage over the first generation vector in human gene transfer. Dr. Noguchi noted that a study on normal humans will provide valuable information.

Dr. Mickelson inquired that if the lung of CF patients is filled up with inflammatory cells, how would the patient's lung be prepared for proper delivery of the vector to the intended target cells? Dr. Crystal said that the patients are first treated with DNase to clear up the airway, and the vector is delivered by bronchoscope to a clean area. Dr. Mickelson asked that if corticosteroid treatment is effective for normal volunteers, will CF patients need to take these drugs for life in order to be treated with the adenovirus vector? Dr. Crystal responded that the aim of corticosteroid administration is to suppress the acute immune reaction to the vector, and it is not intended to be a chronic administration.

Dr. Lysaught noted that immune responses have been observed in normal individuals receiving th intradermal administration of the vector. She asked if a repeat administration as proposed in the Arm B the protocol would deteriorate the situation. Dr. Crystal responded it is likely that the immune responses will be stronger upon repeat administration as predicted from animal studies, however, these immune reactions will not harm the subjects.

Dr. McIvor asked on behalf of Dr. Lai (who left earlier) whether the FDA has approved the amendment to the protocol. Dr. Crystal said that he submitted the request for amendment to both NIH / ORDA and FDA at the same time, and he has not yet received FDA approval.

Dr. Macklin inquired how the normal volunteers are recruited to enroll in the protocol. Dr. Crystal said that advertisements are placed in the local newspaper to recruit volunteers from the Metropolitan New York area primarily the Upper East Side of New York City. Monetary payments to the volunteers are for procedures of bronchoscopies and skin biopsies based on a rate structure used for NIH intramural trial programs. Dr. Crystal noted that in his opinion, it is more ethical to do clinical trials on normals tha sick patients.

Dr. Lysaught stated that she disagrees with Dr. Crystal statement that it is more ethical to do trials on normal subjects. Ms. Rothenberg was concerned about the risk of bronchoscopy , and that the voluntee are paid for the procedure. Dr. Crystal noted that all drugs are evaluated on normal individuals.

Dr. Ando noted that there are many clinical trials involving adenovirus vectors, and it is timely for the RAC

to conduct a general review of the clinical data gathered to date from such studies.

Ms. Rothenberg asked how would Dr. Crystal explain the benefit of the proposed studies on normal individuals to a CF patient. Dr. Crystal said that he is preparing to deliver a speech at the North American Cystic Fibrosis meeting partly aimed at explaining his study to the lay CF patients. The study is trying to understand the normal responses of humans to the adenovirus gene delivery systems so that one can more rationally design the delivery systems or other strategies, such as corticosteroids, to eventually aid all CF patients. Ms. Rothenberg inquired why the lung protocol is preferred for the CF patients than the intradermal protocol. Dr. Crystal explained that the lung protocol is a more realistic study since the lung the major disease organ of the CFpatients

Dr. Aguilar-Cordova noted that in CF patients, there are no neutralizing antibodies in the blood. He asked if it is different from the normals . Dr. Crystal responded that in terms of baseline, there is no difference However, the level is higher after vector administration in normals

Dr. Kapcala (Genetic Therapy, Inc.) commented that corticosteroid at higher doses has been used i many protocols, e.g., oncology protocols. He inquired why not give the subject a higher dose for a longer duration to test its effectiveness. If the cortisteroids work, will the drugs be delivered by aerosol in th future? Dr. Crystal responded that a conservative low dosage is chosen for this study based on his literature survey showing that the proposed dosage is safe for normal subjects. If it is found to be safe, the dosage could be increased and an aerosol delivery could be considered in the future.

Dr. Lysaught asked whether the corticosteroid amendment is necessary since immune response to th vector was observed in CF patients on steroids. Dr. Crystal noted that such observations in 2 patients are anecdotal, and the steroid was administered by aerosol rather than by the systemic route as it is proposed in the amendment. Dr. Crystal emphasized that the proposed study is a rigorous scientific study to evaluate the question of host-vector interactions in humans, and it will provide knowledge for future development of gene therapy.

Dr. Mickelson thanked Dr. Crystal for coming to the RAC and for his responses to concerns raised by the RAC. She noted that there is no need for a RAC vote on the amendment to Protocol 9701-171. The RAC will make a separate decision via e-mail to ORDA regarding whether the intrabronchial proto (9708-209) would require full RAC review. The RAC deadline for such a decision is September 16, 1997.

XI. *POINTS TO CONSIDER* SUBCOMMITTEE/AGUILAR-CORDOVA

Dr. Aguilar-Cordova recommended circulating the preliminary background material regarding revision of Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)* of the *NIH Guidelines*. He said that the subcommittee will be developing a more detailed document for consideration at the December 1997 RAC meeting.

XII. FUTURE MEETING DATES

The next meeting of the RAC will be on December 15-16, 1997, NIH , Building 31C, Conference Room Bethesda, Maryland.

XIII. CHAIR'S CLOSING REMARKS/MICKELSON

Dr. Mickelson noted that the first GTPC was very successful, and a final report of this GTPC will

prepared with inclusion of comments made by the RAC. The second GTPC will be convened on March 1998. Speakers will be invited to present seminars on herpesvirus vectors at the December 15-16, RA meeting.

XIV. ADJOURNMENT/MICKELSON

Dr. Mickelson adjourned the meeting at 4:07 p.m. on September 12, 1997.

Debra W. Knor
Executive Secretary

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

Date: 12/29/97

Claudia A. Mickelson, Ph.D.
Chair
Recombinant DNA Advisory Committee
National Institutes of Health