DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH (NIH)
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
March 6-7, 1997

TABLE OF CONTENTS

The Recombinant DNA Advisory Committee (RAC) was convened for its sixty-sixth meeting at 9:00 a.m. on March 6, 1997, at the National Institutes of Health (NIH), Building 31, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. C. Estuardo Aguilar-Cordova (Acting Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on March 6 from 9 a.m. until 5 p.m. and March 7 from 8:30 a.m. until 4:00 p.m. The following were present for all or part of the meeting:

Committee Members:

C. Estuardo Aguilar-Cordova, Texas Childrens Hospital
Joseph C. Glorioso, University of Pittsburgh
M. Therese Lysaught, University of Dayton
M. Louise Markert, Duke University Medical Center
R. Scott McIvor, University of Minnesota
Claudia A. Mickelson, Massachusetts Institute of Technology
Gail S. Ross, Cornell University Medical Center
Karen Rothenberg, University of Maryland School of Law
Bratin K. Saha, Emory University
Jon A. Wolff, University of Wisconsin Medical School

Executive Secretary:

Debra W. Knorr, National Institutes of Health

A committee roster is attached (Attachment I).

Non-Voting Representative:

Philip Noguchi, Food and Drug Administration

Ad Hoc Consultants:

Eric Juengst, Case Western Reserve University
Nancy King, University of North Carolina, Chapel Hill
Charles McCarthy, Ethics Consultant
Brian Smith, Yale University School of Medicine
Brian Murphy, NIAID

National Institutes of Health staff:

Christine Ireland, OD
Aileen Kelly, DCRT
Becky Lawson, OD
Monique Mansouro, NHGRI
Julie Rhie, NIGMS
Thomas Shih, OD
Sonia Skarlatos, NHLBI
Lana Skirboll, OD

Others:

Paul Aebersold, Food and Drug Administration
Victoria Allgood, GeneMedicine, Inc.
Robert Anderson, Food and Drug Administration
W. French Anderson, University of Southern California
Dale Ando, Chiron Corporation
Cathy Bacquet, Chiron Corporation
Bari Bialos, Cornell Medical Center
Bridget Binko, Cell Genesys

April Birch, Hood College
Paris Burd, Food and Drug Administration
Amy Bosch, Targeted Genetics Corporation
Arindam Bose, Pfizer, Inc.
Andrew Braun, Massachusetts General Hospital
Michelle Brown, Hood College
Jeff Carey, Sandoz Pharmaceuticals
Kevin Conlon, Food and Drug Administration
Kenneth Culver, Codon Pharmaceuticals, Inc.
John Cutt, Schering-Plough Research Institute
Ron Dorazio, Genetix Pharmaceuticals, Inc.
Dean Engelhardt, Enzo Biochem
Diane Fleming, American Society for Microbiology
Jeffrey Fox, Public
Joyce Frey, Food and Drug Administration
Donald Gay, Chiron Corporation
Erin Goley, Hood College
Seeta Gowda, Hood College
Tina Grasso, Genvec, Inc.
Brian Hanshew, Hood College
Lisa Hemmendiger, Public
M. Nielsen Hobbs, The Blue Sheet
Susan Jenks, Journal of the National Cancer Institute
Dorothy Jessup, Public
Kay Justine-Moulton, Food and Drug Administration
Steven Kradjian, Vical, Inc.
Alexander Kuta, Genzyme Corporation
Elliot Marshall, Science Magazine
Andra Miller, Food and Drug Administration
Robert Moen, Baxter Healthcare Corporation
Amanda Bryce Norton, Food and Drug Administration
Lisa Orange, Public
Amy Patterson, Food and Drug Administration
Ioana Petre, Hood College
Theresa Pierson, Contractor, ORDA
Anne Pilaro, Food and Drug Administration
Reginald Rhen, Scrip World Pharmaceutical News
Sharon Risso, Food and Drug Administration
Michael Roy, Geniva
Tomiko Shimada, Ambience Awareness International, Inc.
Sharon Smith, Hood College
Barbara Thenfeld, Enzo Biochem
Jeffrey Weaver, Public
Lisa White, The Blue Sheet
Erin Williams, American Type Culture Collection
Carolyn Wilson, Food and Drug Administration
Robert Zalaznick, Cornell Medical Center

I. CALL TO ORDER AND OPENING REMARKS/DR. AGUILAR-CORDOVA

Dr. Estuardo Aguilar-Cordova (Acting Chair) called the meeting to order and stated that due notice of the meeting and proposed actions under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* were published in the *Federal Register* on February 14, 1997 (62 FR 7108). He noted that a quorum was present and outlined 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. Aguilar-Cordova noted that several new members were present and asked all of the RAC members to introduce themselves: Gail S. Ross, Ph.D., New York Hospital Perinatology Center, New York, New York; R. Scott McIvor, Ph.D., (new member), University of Minnesota, Minneapolis, Minnesota; Jon A. Wolff, M.D., (new member), University of Wisconsin Medical School, Madison, Wisconsin; Claudia A. Mickelson, Ph.D., (new member), Massachusetts Institute of Technology, Cambridge, Massachusetts; CEstuardo Aguilar-Cordova, Ph.D., (new member), Texas Childrens Hospital, Houston, Texas; M. Louise Markert, M.D., Ph.D., (new member), Duke University Medical Center, Durham, North Carolina; Bratin K. Saha, Ph.D., Emory University, Atlanta, Georgia; M. ThereseLysaught, Ph.D., University of Dayton, Dayton, Ohio; and Karen Rothenberg, J.D., University of Maryland School of Law, Baltimore, Maryland.

Dr. Aguilar-Cordova noted that the major agenda items are: (1) the human gene transfer protocol submitted by Drs. Ronald G. Crystal and Ben-Gary Harvey, (2) the generic issues of compliance under the *NIH Guidelines,* (3) the enrollment of normal subjects in gene transfer protocols, and (4) discussion of the *Proposed Actions* published on February 14, 1997, in the *Federal Register*. He stated that the RAC has significantly contributed to the advancement of gene therapy research by providing public oversight and informing the public about the progress of the field. He noted that the RAC has invited several *ad hoc* consultants to address the ethical issues of using normal subjects in gene transfer studies.

II. MINUTES OF THE DECEMBER 9, 1996, RAC MEETING

Committee Motion

The RAC approved a motion made by Dr. Saha and seconded by Dr. Lysaught to accept the minutes of the December 9, 1996, RAC meeting (with the incorporation of minor editorial changes), by a vote of 9 in favor, 0 opposed, and no abstentions.

III. HUMAN GENE TRANSFER PROTOCOL #9701-171 ENTITLED: *IMMUNE RESPONSE TO INTRADERMAL ADMINISTRATION OF AN ADENOVIRUS TYPE 5 GENE TRANSFER VECTOR (AD_{GV}CD.10)*

Principal Investigator: Ronald G. Crystal, M.D., and Ben-Gary Harvey, M.D., New York Hospital-Cornell Medical Center, New York, New York
Reviewers: Lai and Samulski (presented by McIvor), Rothenberg
Written Review--Dr. Lai

In Dr. Lai's written review, he stated that this protocol is designed to study local and systemic immune responses, including humoral and cellular immunity, in normal individuals after the administration of a replication-deficient adenovirus 5 recombinant virus vector. This vector contains an *E. coli* cytosine deaminase (CD) gene. A similar vector was previously used in another protocol, #9509-125, in which the vector was introduced into metastatic colon carcinoma of the liver in a pro-drug treatment in conjunction with oral administration of 5-fluorocytosine (CD which converts 5-fluorocytosine to cytotoxic 5-fluorouracil). The investigator indicated that this particular vector has been administered 10 times to 5

individuals without adverse effects.

Normal, healthy individuals will be recruited into the program with monetary compensation. The subjects will receive either a single dose or multiple doses of the adenovirus vector. For the latter group, multiple doses of the vector will be administered intradermally at 2-week intervals. The subjects will be evaluated by physical examination, blood and urine testings, and lung function testing. Bronchoscopies will be performed on Days 1, 3, 14, 28, and 56. Bronchial Alveolar Lavage (BAL) will be performed to obtain lung epithelial cells. Skin biopsies will be performed on Days 3 and 28, and the biopsy materials evaluated for histology and immunohistochemistry of T cell subtypes, B cells, natural killer T cells, and macrophages. *In situ* hybridization, reverse transcriptase (RT)-polymerase chain reaction (PCR), or Southern blotting analysis will be conducted to evaluate the adenovirus genome. Blood and lung samples will be evaluated for various immunological parameters including antibodies, cytokine production, T cell subsets, and cytotoxic T cells.

Dr. Lai stated that the purpose of this protocol is to study the immunological responses to the adenovirus vector in normal and healthy individuals. These data will provide critical information for tackling one of the major problems in the use of the adenovirus vector, i.e., the immune responses to this virus. The information obtained from this study will provide basic biologic information that will lead to a clearer understanding of adenovirus vectors relevant to gene therapy applications. This protocol raises several new scientific and ethical questions that need to be addressed. Specifically: (1) The potential for systemic infection by the adenovirus vector. He expressed concern about hepatotoxicity and the potential for germ line infection. (2) Will the proposed intradermal route of administration of this adenovirus vector yield information that is useful for future gene therapy involving applications for lung or liver metastasis? He noted that the immune response may vary significantly depending on the route of administration. He asked the investigator to provide the rationale for injecting the virus intradermally to study immune and inflammatory responses in the lung. (3) If the ostensible goal of this protocol is to study the immune responses to the adenovirus vector, why did the investigator choose not to use the empty vector without the transgene? (4) Is animal data available that demonstrates the absence of systemic infection by intradermal injection? (5) If the purpose of this study is to investigate the potential immunogenicity of the vector, is bronchoscopy of the human subject necessary? Antibody responses to intradermal injection may not be relevant to those responses that may be observed in response to bronchial administration. (6) The issues involving the use of normal subjects and potential monetary inducement to recruit subjects should be addressed.

Written Review--Dr. Samulski

In his written review, Dr. Samulski stated that there are no new safety issues related to the use of this adenovirus vector. This vector has been previously reviewed by the RAC (#9509-125) and the Food and Drug Administration (FDA). The primary concern related to this study is the testing for immune responses in the lungs of healthy individuals. The first objective of the protocol, i.e., to determine humoral and cellular immunity to adenovirus vector administered intradermally, will generate valuable information with regard to this reagent and this specific route of administration. However, based on the data provided, there is little rationale for the assays that have been proposed to evaluate the immune response in the normal lung. Unless the investigators anticipate re-administration in this dermal location, the information that they are trying to obtain from this study can be done with techniques less invasive than bronchoscopy. The proposed study puts the patient at undue risk by performing BAL. The same information can be obtained by testing oral (saliva) or rectal mucosa for antibody analysis. It is extremely difficult to evaluate the presence of cytotoxic T lymphocytes (CTLs) in the lung even after primary antigen presentation. Therefore, there is no justification for the protocol to go forward as proposed. This issue should have been addressed by the local Institutional Review Board (IRB). Dr. Samulski recommended

approval of this study after the above concerns relative to the study design have been addressed.

Chair Remarks--Dr. Aguilar-Cordova

Dr. Aguilar-Cordova asked the RAC to defer its comments and questions about generic issues related to the use of normal subjects and compliance under the *NIH Guidelines.* These issues are scheduled for discussion as later agenda items. Discussion of Dr. Crystal's protocol should be limited to the scientific issues related to intradermal administration of the proposed adenovirus vector.

Review--Dr. McIvor

Dr. Aguilar-Cordova called on Dr. McIvor to present the written reviews by Drs. Lai and Samulski in their absence. Dr. McIvor briefly summarized the protocol for RAC discussion. The first concern of Dr. Lai is the potential of systemic infection by the adenovirus vector and the potential for hepatic toxicity. He asked the investigator to address this question with animal and human studies. He noted that both Drs. Lai and Samulski were concerned about the scientific rationale for analyzing the immune response in the lung while administering the virus intradermally and the necessity for conducting bronchoscopies. Dr. McIvor asked the investigator to address the issue of potential systemic viral infection after intradermal injection, and the use of vector and transgene rather than using the empty vector alone. Dr. McIvor noted that the protocol does not provide a description of the assays that will be used to assess the immune responses to the CD transgene product. He asked the investigator to provide present animal data demonstrating the lack of systemic infection in response to intradermal administration of the adenovirus vector.

With regard to Dr. Samulski's review, Dr. McIvor noted that the rationale of analyzing the immune response in the lung after intradermal injection was questioned. He emphasized that the RAC should deliberate on the justification for this protocol to go forward as described. Dr. McIvor asked the FDA representatives to address this issue.

Dr. McIvor summarized the issues that need to be addressed by the investigator: (1) systemic toxicity related to virus as a function of dose, (2) the potential for germ line infection, (3) the scientific rationale for intradermal administration, and (4) a description of the proposed assays for assessing immune responses to CD transgene product. Dr. McIvor noted that the Cornell University Medical College Committee on Recombinant DNA Research assigned a physical containment level of Biosafety Level (BL) 3 for use of the recombinant adenovirus; this adenovirus is classified as a Risk Group 2 human etiologic agent.

Review--Ms. Rothenberg

Ms. Rothenberg raised several issues related to gene transfer, compliance with *NIH Guidelines*, scientific rationale, safety, efficacy, social/ethical context, and the inadequacy of the Informed Consent document. She noted that the original proposal was deemed unacceptable in her preliminary review; however, Dr. Crystal has responded to most of the original concerns relating to scientific and compliance issues in the written response. Dr. Crystal has made a good faith attempt to address the Informed Consent document concerns; however, several Informed Consent document issues still remain. Specifically, the scientific basis for performing bronchoscopy and skin biopsy after intradermal administration remains unclear. The purpose of the study has not been adequately explained in the Informed Consent document. She expressed concern about the use of the term "treatment" to describe this procedure and the use of the phrase "your physician or your doctor" in the context of normal individuals. She stated that the language should be clarified with regard to the purpose of administering the $AD_{GV}CD.10$ vector. The phrase "vaccination type" should be clarified. The potential for systemic viral spread and potential risk to the subject should be clearly explained. The potential for developing keloids and a scar at the biopsy site

should be clearly stated. The number of biopsies that will be performed should be clarified. A paragraph should be included informing potential subjects about a fatality that occurred in 1996 related to an overdose of lidocaine in one subject undergoing bronchoscopy. Ms. Rothenberg questioned the necessity for conducting bronchoscopies in the proposed studies. Have the risk versus benefit issues been carefully examined? Regarding monetary compensation to these normal volunteers, coercion may be an issue of concern. The timing of the follow-up procedures, i.e.,bronchoscopy should be clearly described because normal subjects have concerns related to necessary daily activities, e.g., jobs. She expressed concern about coercion of normal individuals to participate in the study based on monetary inducement. The payment plan has been revised in response to her preliminary review ($900 rather than $1000 as initially proposed), by deleting the bonus offered to the participants to complete the follow-up procedures. The original compensation plan was inconsistent with being allowed to withdraw participation at any time during the protocol.

She stated that the protocol does not offer long-term follow-up and any plan of autopsy; she recognized the difficulty of informing normal individuals of the necessity for such requests; however, these issues should be addressed.

Other Comments

Dr. Saha stated that normal subjects are already involved in many clinical studies. His major concerns are related to the scientific rationale of the proposed study. The use of normal subjects to evaluate the immune response to the adenovirus vector presents a scenario different from applications for diseases such as cystic fibrosis (CF) and cancer which have different immunological background. Disease applications will require different transgenes; perhaps the empty vector should be used alone, without the transgene. Dr. Saha questioned whether the intradermal route would yield relevant information for protocols administering the virus by other routes; the rationale forbronchoscopy following intradermal administration is doubtful.

Dr. Markert said that some immune responses tointradermal vector administration are detectable in the BAL fluid samples of the lung due to systemic immune response, but for a gene therapy application directed at airway epithelial cells, it would be preferable to administer the vector directly to the lung. The Informed Consent document should clearly state the number of visits required and the amount of blood that will be withdrawn at each visit. She asked for clarification of the funding source of this protocol.

Dr. Ross inquired how the information obtained from normal subjects will be used to plan future applications involving patients with specific diseases. The generic issues involving the use of normal individuals in gene therapy studies should be addressed.

Dr. Aguilar-Cordova stated that the generic issue of normal subjects will be a separate discussion. Dr. Lysaught noted that such a discussion is relevant to the approval of this protocol based on the fact that the present protocol will not provide any benefit to the participants. Dr. Aguilar-Cordova responded that the issue of benefit to subjects is not different from that of gene marking protocols. DrLysaught noted that gene marking studies are conducted in conjunction with treatment of other diseases, usually with limited life expectancy; the risk/benefit ratios are not the same as for the present protocol.

Dr. Aguilar-Cordova noted that there are second and third generation of adenovirus vectors that have been developed which are greatly improved over this first generation vector; he questioned the scientific value of testing this older generation vector. The presence of the CDtransgene in the construct may complicate evaluation of immune responses to the vector.

Dr. Wolff noted that sensitization of the normal individuals to the adenovirus vector might prevent them from participating in future adenovirus protocols. Human immunological data are available from many other adenovirus vaccine studies conducted in the past with army recruits.

Dr. Mickelson agreed that data on wild-type adenovirus are available, and there is no need to conduct another study with this recombinant virus. Immunogenicity of the CD transgene should be investigated to make sure it does not have superantigen properties. Immune responses may be different in normal subjects than in subjects with disease. The route of administration may be a significant variable.

Dr. Aguilar-Cordova asked Dr. Miller to provide the FDA perspective on approval of such protocols. Dr. Miller responded that FDA's major concern for Phase I protocols is safety assessment. Each protocol is evaluated by 3 scientific reviewers: product, clinical, and pharmacology/toxicology. FDA evaluates safety of the product as well as risk/benefit to the subjects. Drs. Saha and Ross inquired if the FDA considers the scientific rationale for conducting the study. Dr. Miller responded that for a Phase I study, safety is the primary concern.

Investigator Response--Dr. Crystal

Dr. Crystal gave a slide presentation to respond to issues raised by the RAC. He stated that he received Investigational New Drug (IND) approval from the FDA prior to submission to the Office of Recombinant DNA Activities (ORDA) and the Institutional Biosafety Committee (IBC). Dr. Crystal explained that this oversight in compliance with the *NIH Guidelines* was not intentional, as the delay related to the holiday season and the availability of personnel.

Dr. Crystal explained that this protocol is similar to a vaccine study except the CD transgene is inserted in the construct. The construct is currently being used in a cancer protocol, #9509-125. In that trial, no toxicity was observed in the 5 subjects who have received the vector by intratumoral injection to colon cancer liver metastasis at doses identical to the maximum dose proposed in the present protocol. The study is designed to answer basic biologic questions regarding characterization of immune responses to the vector, i.e., at a local site (skin), a systemic compartment (blood), and a distant compartment (lung). H stated that he and his colleagues have performed over 5,000 bronchoscopies with lavage in the last 20 years on 1,000 normal subjects. All of the clinicians involved are very experienced with this procedure.

Dr. Crystal said that he has prepared a very similar proposal for administration of the adenovirus vector directly to the lung. This intradermal protocol was submitted first because this route of administration is believed to be a safer approach than direct lung administration, particularly, for normal subjects.

Responding to the question about using this first generation adenovirus vector, Dr. Crystal said that there is little animal data demonstrating that newer generation vectors offer any significant advantage. The present vector will most likely have the same clinical applicability as the later generation vectors. This baseline information derived from this first generation adenovirus is critical to compare the efficacy of other variations in vector design.

In regard to the immune response assays, he stated that humoral and cellular immunity will be assessed and vector-induced inflammation will be evaluated. Humoral immunity will be assessed by assaying blood and lung epithelial cells for neutralizing antibodies against the adenovirus vector and the CD transgene product. Cellular immunity against the adenovirus vector and CD transgene will be evaluated in local, systemic, and distant compartments.

Dr. Crystal emphasized the importance of conducting this adenovirus study in humans. Animal studies

suggest that Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) transgene expression is expected to last less than three months in humans. Intradermal administration is probably the safest paradigm to test the immune response in humans. Allergy testing in humans generally requires intradermal injection of a variety of substances. Intradermal sites are easily biopsied to study the immune response as a function of time.

With regard to the use of normal subjects, the enrollment of normal volunteers is standard practice in clinical research. FDA regulations provide guidance on the use of normal subjects in Phase I drug development trials.

One example as to the importance of conducting normal human trials is the previous CF gene transfer trial. In that Phase I trial, an adverse event was observed in very sick subjects. This adverse reaction was not expected from the preclinical animal studies. The severe lung inflammation that occurred was not observed in primate studies at doses 1,000-fold higher than those doses used in humans. Another example of how preclinical animal studies do not accurately predict human responses was observed in the repeat dosage CF trials. Neutralizing antibodies were not detected in patients lungs; however, animal data suggested a high level of neutralizing antibodies should be detected.

Dr. Crystal stated that normal subjects may be the only individuals capable of giving true consent to participate in a clinical research trial since they do not have disease and are not expecting any benefit from the experimental procedure. Patients with serious diseases, such as CF or cancer, are likely to have some thought of benefit even though they are informed that the treatment will not be beneficial. He presented a slide to illustrate the difficulty in determining a "normal" subject. There is a continuous spectrum of severity of disease. For example, a CF patient who is a compound heterozygote with two mild mutations, will probably have a normal life span. A similar scenario can be observed in some cancer patients who are virtually "normal" (disease-free) following removal of their tumor.

In response to questions of potential risk to normal subjects, he stated that intradermal administration should present minimal risk. The doses proposed have been given previously to hepatic cancer patients with no adverse effects. A similar vector was used in the CF protocol with a different transgene at 10-fold higher doses with no toxicity. With regard to questions about use of the CD transgene, CD is a bacterial gene not found in humans. Use of this CD vector is economically preferable, because it has been used extensively in animal studies. In addition, information about immunity to the CD transgene will be available from this study. Responding to Dr. Lai's question about liver toxicity, Dr. Crystal presented murine data from studies using the clinical grade vector expressing the CD transgene. When administered intravenously at doses 1,000-fold higher than the proposed human dose, no liver toxicity was observed.

Dr. Crystal presented animal data addressing the issue of germ cell infection. The vector was given at 10-fold higher doses than those proposed for the human study (per kilogram body weight). Gene transfer to the gonads was not detected by PCR assay. He stressed that there has been no evidence to date that adenovirus genes are transmitted through the germ line in humans. Over 95% of the human population has been infected with adenoviruses. Adenovirus infection is episomal; therefore, there is no risk of insertional mutations. He stated that except for the question of potential germ line infection, adenoviral vectors are similar to other types of drug development. Typically, between 20 and 80% of Phase I trials are conducted using normal volunteers.

Dr. Crystal responded to questions about compensation of normal volunteers. He explained that it is a standard practice to compensate normal volunteers participating in clinical research. The subjects are compensated for their inconvenience. He cited the NIH Clinical Center program in which NIH recruited

3,500 normal volunteers and made 6,100 payments to the volunteers with a total compensation of over $800,000 in 1996. Dr. Crystal said that the monetary compensation for this protocol is within the standards of the NIH intramural clinical program.

Dr. Crystal presented data derived from murine toxicity studies. No liver toxicity was observed after intravenous administration of the clinical grade vector at a dose of 1,000-fold higher than the dose for the human study. He emphasized that the murine intravenous experiments are intended to represent a worst case scenario since 90% of the vector goes to the liver. Most other studies published in the literature have not been performed using clinical grade vector which has no replication-competent virus (RCV) contamination (less than one particle per total dose of 10^9 particles).

Dr. Crystal explained that the scientific rationale of conducting this proposed study is to obtain information about adenovirus immunity. More than 5 million military recruits have received oral (non-recombinant) adenovirus vaccines. Very little information has been published in the literature regarding immune reactions except one report describing CTL against the E1A epitope. Recombinant adenovirus used for gene therapy clinical trial contain an E1A deletion. The lack of published data on adenovirus immune responses is the purpose of the proposed study.

Dr. Saha inquired if CTL responses have been observed in the colon carcinoma trial. Dr. Crystal responded CTL responses were not detected. Dr. Crystal presented data from a murine study involving the CD transgene and the empty vector. These techniques will be used to evaluate CTL responses in the human study. In the murine study, CTL responses against the CD transgene were observed; a result different from the human colon carcinoma study. These differences between animal and human responses to the CD transgene is the basis of the proposed human study.

Dr. Markert asked for further clarification about the scientific rationale. She noted that human immune responses are variable and questioned the extent to which the data was obtained from the proposed intradermal trial will yield valuable information for future trials in CF patients. Dr. Crystal responded that multiple routes of administration will be proposed; these other protocols are currently in preparation. It is preferable to study differences in immune responses to various routes of vector administration because of immune response compartmentalization.

Dr. McIvor emphasized that the scientific rationale for this study requires further clarification. Dr. Crystal explained that the primary rationale for this proposal is to obtain information pertaining to the basic biologic question of how humans respond to adenovirus administration; he noted the need to contribute to this information base using adenovirus vectors administered to various sites. This information base will be critical to the development of future generations of adenovirus vectors and for evaluation of the immunosuppressive drugs used to minimize the effects of these immune responses. Normal human subjects will be particularly valuable for this latter study. Dr. McIvor asked Dr. Crystal to explain the rationale for performing bronchoscopies following intradermal rather than lung administration. Dr. Crystal responded that the intradermal study is being proposed first because it is a safer approach, especially because normal subjects will be involved. He noted that the lung protocol is in preparation. Dr. Crystal stated that in his opinion, the proposed bronchoscopies are a safe approach that will provide valuable mucosa immunity data.

Ms. Rothenberg asked if Dr. Crystal would start his next lung study after the data from the present skin protocol are evaluated. Dr. Crystal responded that he would prefer this kind of deliberate approach. Ms. Rothenberg asked why the present study was not limited to examining the skin reaction. Dr. Crystal responded that the bronchoscopy data is essential; there is very little information regarding immune reactions in the lung.

Dr. Saha inquired if subjects will be selected based on previous adenovirus exposure. Dr. Crystal responded that the inclusion criteria include demonstration of a neutralizing antibody titer of less than 1 to 20.

Dr. McIvor asked Dr. Crystal to respond to questions about the potential for viral spread to other organs and whether the experiment needs to be conducted under BL3 physical containment as recommended by the IBC. Dr. Crystal explained that the IBC assignment of BL3 containment is an apparent mistake. He will seek correction; the containment level should be BL2 instead of BL3. Dr. Crystal stated that he has investigated all organs including gonads by a sensitive PCR assays; no viral spread has been detected in animals. No viral shedding has been observed after lung or liver administration.

Responding to Ms. Rothenberg's comments about the Informed Consent document language, Dr. Crystal said that he followed the model document developed by the IRB. Ms. Rothenberg said that to use the term "treatment" for normal subjects is not appropriate. Dr. Crystal agreed to modify the Informed Consent document accordingly, including clarification regarding the number of biopsies expected. With regard to the unfortunate fatal lidocaine incident during the conduct of a bronchoscopy procedure in Rochester, New York, Dr. Crystal emphatically stated that this kind of accident would not occur in his hospital based on the standard operating procedures and his vast experience, over 5,000 bronchoscopies on over 1,000 normal subjects.

Dr. Crystal responded to other comments regarding the Informed Consent document. The reason that the specific number of procedures was not rigidly specified in the Informed Consent document is to allow a certain degree of flexibility to accommodate the specific availability of participants. Payments are intended to compensate for inconvenience, it is very difficult to track down normal subjects and obtain long-term follow-up. Ms. Rothenberg cited an example of an autopsy statement used in a CF protocol, "In the case of an unexpected death such as from a car accident, a postmortem evaluation would be valuable to search for any effects. My participation means that I would tend to favor an autopsy should such an occurrence taken place. I will notify my family of my opinion." Dr. Crystal said that if the RAC insists on this requirement, he would put similar language in his Informed Consent document.

Dr. Lysaught stated that long-term follow-up is important in order to evaluate long-term health risks, e.g., oncogenic potential, particularly for normal subjects. Dr. Crystal responded that adenoviruses do not insert into the host cell genome; therefore, the risk of developing cancer is minimal.

Dr. Wolff raised the issue of long-term immunity against either the adenovirus or the transgene which could prevent treated persons from receiving adenovirus gene transfer in the future. He stated that the Informed Consent document should contain a statement to that effect.

Dr. Saha stated that most of the information to be obtained from this protocol should be available from the previous human adenovirus trials; he asked why a study of normal individuals will yield specific new information for CF protocols. Dr. Crystal responded that it is basically an academic inquiry to address the basic biologic question. Dr. Wolff asked if FDA has experience with investigators proposing an analogous generic experiment in Phase I drug trials. Dr. Miller responded that if the experiment would provide useful information for the design of their final plan for drug development, then FDA would accept such a proposal. Dr. Aguilar-Cordova asked Dr. Crystal to explain his study along this analogy. Dr. Wolff asked how this study will benefit future specific studies, e.g., CF protocols. Dr. Crystal repeated his statement that the study will yield basic information for future adenovirus vector development, e.g., long-term transgene expression. He emphasized that intradermal administration is the safest route for normal people.

Dr. Lysaught noted that the requirement for subjects to be isolated between 24 and 48 hours following vector administration is probably a burden to most normal individuals. Dr. Crystal agreed to her statement that patient isolation is a burden. He would clarify the discrepancy of whether it should be 24 or 48 hours.

Dr. Ross questioned the added value of conducting the study with normal subjects as opposed to studying the immune responses specific to individuals with certain types of disease. Dr. Crystal responded that normal individuals have no disease specific variables to complicate the study.

Dr. Markert commented that the study may serve as a model system to assess whether a lung immune response will occur if the vector is administered to the skin. If there is no lung reaction, the vector can be given to the lung subsequently. This observation may benefit the study to assess systemic effect of thrombopoietin complementary DNA (cDNA) administered to the skin, an experiment Dr. Crystal alluded to in his earlier remarks. Dr. Markert stated that studies of normal individuals' immune reactions will benefit adenovirus vector development. Dr. Aguilar-Cordova said that from the immunology standpoint, he still has a concern that different responses to different vectors may not provide conclusions that areapplicable to all vectors.

Committee Motion 1

Dr. McIvor proposed a motion to approve the protocol contingent on: (1) providing a description of the assays to assess the immune response to the CDtransgene product, (2) inclusion of a statement in the Informed Consent document regarding the potential limitation of subjects treated in the protocol from participating in future adenovirus studies, and (3) other changes to the Informed Consent document suggested by Ms. Rothenberg. Dr. Mickelson seconded the motion.

Dr. Wolff made a friendly amendment to ask Dr. Crystal to make a good faith effort to assay germ cells for the presence of vector sequences using sensitive assays, e.g.,PCR analysis. Dr. McIvor stated that the amendment is a major change of the protocol, and he suggested that the RAC should vote on it as a separate motion.

Ms. Rothenberg stated that the RAC should vote on this protocol after hearing the testimony by the ethics consultants. Dr. Aguilar-Cordova asked Ms. Rothenberg to make a motion to defer the vote until the ethics discussion. Dr. McIvor agreed; he said that Ms. Rothenberg's motion to table the vote on protocol approval should be considered first.

Ms. Rothenberg proposed a motion to table the committee vote of the protocol until after discussion by the *ad hoc* ethics consultants. Dr. Saha seconded the motion.

Committee Motion 2

A motion was made by Ms. Rothenberg and seconded by Dr. Saha to table the motion made by Dr. McIvor to approve Dr. Crystal's protocol until after the discussion with the *ad hoc* consultants that were invited to discuss the ethical issues raised by proposing gene transfer in normal subjects. The motion passed by a vote of 7 in favor, 0 opposed, and 2 abstentions. Dr. Ross abstained due to conflict of interest; she is employed by the same institution.

Dr. Crystal expressed his concern that he had not been informed that *ad hoc* ethics experts were invited to discuss his protocol; his understanding was that the generic discussion of ethics issues would be held separate from approval of his protocol.

Dr. Wolff proposed a motion to require the investigators to make a good faith effort to determine if there is any germ line effect of the protocol. Dr. McIvor seconded the motion. Dr. Crystal stated that it is a very cumbersome request to ask normal individuals to provide sperm samples to perform the assays; nevertheless, he agreed to make a good faith effort to perform such studies. Ms. Rothenberg said that such a study is important. Dr. Crystal agreed to the good faith effort and said that a subject's willingness to donate a sperm sample should be voluntary rather than mandatory.

Committee Motion 3

A motion was made by Dr. Wolff and seconded by Dr. McIvor to require the investigators to make a good faith effort to perform analysis on patients to monitor for transmission of the adenovirus vector to the germ cells in normal subjects, e.g., sperm samples. The motion passed by a vote of 6 in favor, 1 opposed, and 2 abstentions.

IV. CONTINUED DISCUSSION OF PROTOCOL #9701-171--AD HOC CONSULTANT DISCUSSION OF ISSUES INVOLVING NORMAL SUBJECTS

Ms. Knorr introduced 3 *ad hoc* consultants who were invited to discuss the ethical issues raised by gene transfer research conducted in normal human subjects: (1) Dr. EricJuengst, Associate Professor of Biomedical Ethics at Center for Biomedical Ethics, Case Western Reserve University, Cleveland, Ohio; (2) Dr. Charles McCarthy, Ethics Consultant of Richmond, Virginia; and (3) Ms. Nancy King, Associate Professor of Social Medicine at University of North Carolina, Chapel Hill, North Carolina.

Dr. Aguilar-Cordova asked the *ad hoc* consultants to address issues pertinent to the approval of Dr. Crystal's human gene transfer protocol.

Dr. Juengst stated that it was his understanding that the RAC has approved many gene transfer protocols on the premise that the human subjects were critically ill patients, i.e., they are a relatively risk free pool of subjects for clinical research. One of the problems encountered when dealing with such sick patients is that it is difficult to make an independent and informedjudgement about participating in a clinical trial which offers no direct benefit to their illness. Dr.Juengst said that it is acceptable to use normal volunteers for this kind of study that offers no benefit. CF patients would likely be confused more easily; believing that the procedure might have some therapeutic benefit.

Dr. McCarthy stated that he worked at theNIH for many years and has been involved with many controversial cases involving ethical questions raised by clinical trials. Traditionally, normal volunteers have been included in clinical studies, whenever the research was deemed appropriate. For most clinical research studies, normal volunteers are preferable over sick patients, who can sometimes be compromised by their diseases. The involvement of normal volunteers has to be justified in terms of the knowledge that will be gained because they will not receive any direct benefit from their participation in the clinical trial. Dr. McCarthy stated that the question of scientific rationale of the protocol should be a critical focus of the RAC's discussion. He noted that the Informed Consent document describes the risk of bronchoscopy and the previous fatal incident related to this procedure very well; however, the discomfort associated with the bronchoscopy procedure is very understated. There are 5bronchoscopies that will be performed on each subject. The RAC should consider whether the proposed research is important enough to justify putting subjects through this level of discomfort. He said that he does not have any objection to the monetary compensation proposed; this amount is consistent with the accepted clinical practices in the United States.

Ms. King stated that she agreed with statements made by Drs. Juengst and McCarthy. She pointed out that the issue of risk and benefit to subjects participating in gene transfer protocols has existed in previous RAC approvals, but it has not become an outstanding issue simply because the issue has been framed in the therapeutic context of studies involving subjects with diseases. Ms. King recommended that the RAC should revisit Appendix M, *The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider)* of the *NIH Guidelines* regarding the use of normal subjects for gene transfer studies.

V. CONTINUED DISCUSSION OF PROTOCOL #9701-171--COMMITTEE MOTION

Dr. Aguilar-Cordova called on Dr. McIvor to restate his motion to approve Dr. Crystal's protocol. Dr. McIvor stated that the motion was to recommend approval of the protocol contingent on: (1) inclusion of assays to quantitate the immune response to the CD gene, (2) modify the Informed Consent document regarding the potential limitation of participating in future adenovirus vector trials, (3) changes of the Informed Consent document specified by Ms. Rothenberg, and (4) requirement of the investigators making a good faith effort to assess germ line transmission. Dr. Mickelson seconded the motion.

Ms. Rothenberg asked Dr. Crystal if it is clearly understood what changes need to be made regarding the Informed Consent document, e.g., assays of sperm samples for vector sequences and autopsy. Dr. Crystal responded that he would make the appropriate amendments to the Informed Consent document. Dr. Saha stated that the subjects should be informed about the discomfort of undertaking the bronchoscopy procedure.

Dr. Lysaught proposed a friendly amendment to state that this protocol is being accepted as an independent protocol, and it should not be considered as a precedent for a general use of normal volunteers for gene transfer studies. Ms. Rothenberg seconded the friendly amendment. Dr. McIvor accepted the friendly amendment.

Committee Motion 4

A motion was made by Dr. McIvor and seconded by Dr. Mickelson to recommend approval of the protocol submitted by Dr. Ronald G. Crystal, New York Hospital-Cornell Medical Center, New York, New York. The RAC's recommendation for approval is contingent on review and approval of the following by the RAC reviewers and the NIH Director: (1) a description of the assays that will be conducted to assess the immune response to cytosine deaminase, (2) inclusion of language in the Informed Consent document regarding the potential that the subjects' participation in future adenovirus protocols may be limited based on their exposure to the Ad_{GV}CD.10 adenovirus vector, (3) incorporating the changes suggested by Ms. Rothenberg in the Informed Consent document, (4) making a good faith effort to assay germ cells for the presence of vector sequences by e.g., PCR assays, and (5) approval of this protocol should not be construed as a precedent for accepting any other general use of normal volunteers for gene transfer studies. The motion passed by a vote of 6 in favor, 1 opposed, and 2 abstentions.

Dr. Ross noted that the protocol is novel in a sense that it is neither a gene marking nor a gene therapy protocol.

Protocol Summary

Contingent on the NIH Director's approval, Dr. Ronald G. Crystal of New York Hospital-Cornell Medical Center, New York, New York, may conduct gene transfer experiments on a total of 21 (with an option for an additional 5) normal male or female subjects, age _18 years. Replication-deficient adenovirus (Ad)

vector have previously been used in a number of human gene therapy strategies to transfer genes *in vivo* for therapeutic purposes. The purpose of this protocol is to characterize the local (skin), systemic (blood), and distant compartment (lung) immunity in normal individuals after intradermal administration of a replication deficient Ad5-based vector, named $Ad_{GV}CD.10$, carrying the gene coding for the *E. coli* enzyme, CD. Following intradermal administration of the vector to normal individuals, the skin, blood, and lung immune responses to the Ad vector and CD transgene will be evaluated over time. This vector has been safely administered intrahepatically ten times to five individuals with colon carcinoma. No adverse effects in Protocol #9509-125 have been observed. The present protocol will yield basic biological information about normal human immune responses to both the Ad vector and the heterologous (i.e., non-human) gene product, cytosine deaminase.

VI. PROPOSED AMENDMENTS TO APPENDIX B , *CLASSIFICATION OF HUMAN ETIOLOGICAL AGENTS ON THE BASIS OF HAZARD* OF THE *NIH GUIDELINES*/**SHIH**

***Ad Hoc* Consultant: Dr. Brian Murphy, NIH**

Dr. Aguilar-Cordova called on Dr. Shih to introduce the proposed amendments to Appendix B. Dr. Shih explained that Appendix B of the *NIH Guidelines* provides guidance to IBCs, biosafety officers, and investigators for the purpose of ensuring the safe conduct of recombinant DNA experiments involving human etiologic agents. Appendix B was extensively revised in 1995. At that time, the RAC stipulated that a special committee of the American Society for Microbiology (ASM) should conduct an annual review of Appendix B and report any recommendations regarding changes to the RAC as proposed amendments to the *NIH Guidelines*.

In a letter dated December 2, 1995, Dr. Kenneth I. Berns (President), Dr. Gail Cassel (Chair, Public and Scientific Affairs Board), and Dr. Diane O. Fleming (Chair, Subcommittee on Laboratory Safety) of ASM requested that Equine morbillivirus, Sabia, and Flexal be added to Appendix B. The Centers for Disease Control and Prevention (CDC) has developed a list of select agents identified as potential weapons for biological terrorism. These select agents are subject to a Federal regulation, 42 CFR Part 72, published by CDC on October 24, 1996, in the *Federal Register* (61 FR 55190). This regulation promulgates the final rule of additional requirements for facilities transferring or receiving select agents. Most of the biological agents in the select agents list are already included in Appendix B except these 3 viruses being requested for inclusion by ASM.

In a letter dated December 20, 1996, ORDA asked Dr. Diane Fleming, ASM, to clarify the proper Risk Group classification of these 3 viruses. In her letter dated February 3, 1997, Dr. Fleming stated that Flexal virus should be listed as a Risk Group 3 agent based on the classification recommended in a CDC/NIH publication entitled: *Biosafety in Microbiological and Biomedical Laboratories*, 3rd Edition, 1993. Sabia virus and Equine morbillivirus have not been formally classified in this publication. Dr. Fleming stated that she has consulted with Dr. Michael P. Kiley, Chairman of the Subcommittee on Arboviral Laboratory Safety (SALS) of the American Society for Tropical Medicine and Hygiene with regard to the proper Risk Group classification of these 2 viruses. Dr. Kiley recommended that Sabia and Equine Morbillivirus should be classified as Risk Group 4 agents. Risk Group 4 agents are handled under BL4 physical containment, because they are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not available.

The ASM requested other minor corrections of Appendix B as follows: (1) Appendix B-II-A. *Neisseria gonorrhoea* is missing the final "e" on the species name. It should read as *Neisseria gonorrhoeae*. (2) Appendix B-IV-D. Remove the erroneous reference to "Togaviruses - Group A Arboviruses" from the virus family name of "Arenaviruses." (3) Appendix B-II-B. *Blastomyces dematitidis* is missing an "r" in the

species name. It should read as *Blastomyces dermatitidis*. (4) Appendix B-II-A. *Acinetobacter baumannii* (formerly *Acinetobacter calcoaceticus*) should read as *Acinetobacter baumannii* (formerly *Acinetobacter calcoaceticus* var. *anitratus*). In a letter dated February 19, 1997, Dr. Fleming withdrew this request stating that the *A. baumannii* appears to be the genomic species of greatest clinical significance and it is the species most frequently isolated from clinical sources.

Review--Dr. Murphy

Dr. Murphy concurred with the ASM request to amend Appendix B to include Equine morbillivirus, Sabia, and Flexal in Appendix B. He concurred with the assignment of Flexal as a Risk Group 3 virus listed in Appendix B-III-D, *Risk Group 3 (RG3) - Viruses and Prions*, and Sabia and Equine morbillivirus as Risk Group 4 viruses in Appendix B-IV-D, *Risk Group 4 (RG4) - Viral Agents*. His opinion is based on the following information:

(1)Equine morbillivirus is a paramyxovirus that has produced lethal disease in humans, horses, and cats (Gould, A. R., *Virus Research 43(1)*, 17-31, 1996; Westbury, H. A. et al., *Aust Vet J., 74(2)*, 132-134, 1996; Rogers, R. J. et al., *Aust Vet J, 74(3)*, 243-244, 1996). Like other members of the morbillivirus group (e.g., measles virus, canine distemper virus, and rinderpest virus), it is infectious by the respiratory route; causes pneumonia; and can spread systemically. It is thought to be azoonosis with fruit bats as a reservoir. Dr. Murphy noted that this virus was recently identified in an outbreak involving a horse and its veterinarian, both died of the infection. It should be classified as a Risk Group 4 agent requiring BL4 physical containment.

(2)Sabia virus is a South American arenavirus that is a member of a group of Arenaviruses that cause hemorrhagic fever in humans (Gonzales, J. P. et al., *Virology, 221(2)*, 318-324, 1996; Fulhorst, C. F. et al., *Virology, 224(1)*, 114-120, 1996). It was first isolated from a fetus in 1990 and has since caused 2 cases of severe illness in laboratory workers (Lixieux, T. et al., *Lancet, 343(8894)*, 391-192, 1994; Arenavirus infection--Connecticut, *MMWR Mobility Mortality Weekly Report, 43(34)*, 635-646, 1994, and a published erratum in *MMWR Mobility Mortality Weekly Report, 43(35)*, 659, 1994). It can be transmitted by aerosol. It is thought to be a zoonosis with rodents as a reservoir. This virus causes hemorrhagic disease, and it has been associated with laboratory infections. It should be classified as a Risk Group 4 agent.

(3)Flexal is a South American arenavirus. Although it has not been associated with any fatal human diseases, laboratory infections have been identified. Flexal's pathogenic potential has not yet fully described. Other strains of these South American arenaviruses cause severe infections in humans. Dr. Lysaught inquired about the severity of the laboratory infection that was observed. Dr. Murphy responded that he was unable to find a published report on the symptoms of this viral infection.

Dr. Aguilar-Cordova inquired if the request is for the reclassification of these viruses. Dr. Fleming who is a co-signer of the ASM request letter, explained that Equine morbillivirus and Sabia have not been previously classified. The Flexal virus has been classified as a Risk Group 3 virus in the CDC/NIH publication entitled: *Biosafety in Microbiological and Biomedical Laboratories*, 3rd Edition, 1993.

In a written review dated January 27, 1997, Dr. Stephen E. Straus, NIH, stated that he concurred with the technical corrections to Appendix B suggested by Drs. Berns, Cassel, and Fleming. He concurred with their recommendation that Flexal be added as a Risk Group 3 agent and that Sabia and Equine morbillivirus be added as Risk Group 4 agents. More generally, Dr. Straus recommended that the RAC could receive, review, and accept SALS recommendations directly regarding classification of the Arboviruses.

Committee Motion 5

A motion was made by Dr. Markert and seconded by Dr. Lysaught to include Flexal, an arenavirus, to Appendix B-III-D, *Risk Group 3 (RG3) - Viruses and Prions*, and Sabia, an arenavirus, and Equine morbillivirus, a paramyxovirus, to Appendix B-IV-D, *Risk Group 4(RG4) - Viral Agents*. The motion passed by a vote of 8 in favor, 0 opposed, and no abstentions.

VII. DISCUSSION REGARDING GENE TRANSFER PROTOCOLS INVOLVING NORMAL SUBJECTS

VII-A. Historical Perspective - Use of Normal Subjects in Clinical Research

Dr. Aguilar-Cordova called on Dr. Juengst to expand his thesis on the use of normal human subjects for gene transfer studies. Dr. Juengst stated that he will address the concerns expressed by several RAC members that the entertainment of protocols involving normal individuals would open the door to entertaining protocols for enhancement interventions. The discussion of treatment versus enhancement types of clinical protocols was historically deliberated in the area of gene transfer studies; Dr. Leroy Walters, former Chair of the RAC, was a leader in these bioethics discussion. Dr. Juengst said that he himself was recently involved in two research projects attempting to delineate the treatment/enhancement distinction.

Dr. Juengst explained that enhancement intervention would be an intervention that would give the subjects capabilities that go beyond the normal human range of typical capabilities. Conversely, treatment is considered an intervention that is designed to raise an individual's capabilities from below normal to the normal range. Dr. Juengst said that the RAC has already crossed the enhancement bridge by approval of James Wilson's hypercholesterolemia protocol (#9110-012), in which the low density lipoprotein receptor was boosted to the above normal range by a gene transfer procedure. The patients were given super cholesterol cleansing ability that enhances their ability to clear cholesterol from the blood due to the genetic condition that manifests hypercholesterolemia. This protocol was approved by the RAC in the context of therapeutic intervention. It is an enhancement aimed at treating a disease. Many cancer immunization protocols belong to this category.

Dr. Juengst noted that most of the current ethics studies that aim to distinguish the preventive interventions from the enhancement interventions address social rather than health goals. The area of most concern is enhancement interventions for the purpose of improving one's social position, e.g., to improve one's appearance or athletic capability. Dr. Juengst noted that the distinction between treatment and enhancement is not sufficiently clarified for policy making purposes regarding gene transfer protocols. One needs to define the types of interventions that should be encouraged and the types of interventions that are morally troubling. To draw the line of distinction between treatment and enhancement is a challenge to amend the Appendix M, *Points to Consider,* regarding gene transfer protocols.

Dr. Aguilar-Cordova called on Dr. McCarthy to continue the discussion on the use of normal subjects in gene transfer protocols. Dr. McCarthy stated that the first human subjects policy in the United States was written in 1953. This policy governed research involving normal volunteers. At that time, there was no formal policy applicable to patient subjects; the relationship between investigators and sick individuals was governed by the doctor-patient relationship. Normal volunteers have always enjoyed a special protection. Ethical theory regarding normal subjects in clinical research is difficult to apply because the risks to normal volunteers are justified only in terms of the knowledge to be gained, i.e., benefit to society as a whole but not to individuals. To arrive at a consensus position about research that is deemed acceptable, many disinterested parties must be consulted. Such decisions should be made on a case-by-case basis since the benefit/risk consideration varies with each case. Dr. McCarthy noted that the

RAC's vote on Dr. Crystal's protocol highlights this point. The RAC arrived at its consensus position by a vote. That vote was based on consideration of the knowledge that would be gained from the study versus the risk or discomfort that subjects would endure. It is important to note that the RAC formally stated that approval of this protocol should not set a precedent for the general use of normal volunteers in gene transfer studies.

Dr. McCarthy noted that Dr. Crystals Informed Consent document clearly stated the potential risk, subjects have the option to withdraw from the study if they find that the bronchoscopies are intolerable. However, the justification for taking these risks has not been clearly articulated. Subjects will choose to participate in this study by their own volition; therefore, it is unethical to involve them in this research unless knowledge will be gained that will benefit society as a whole, regardless of the amount of financial compensation. A statement regarding the overall social benefit of the study should be clearly stated to the subjects.

Ms. King noted that with regard to Dr. Juengst's statement that the RAC has crossed the bridge of transferring genes to normal subjects, it is important to note that although this bridge was crossed, the bridge could be re-crossed again if necessary. She agreed with Dr. McCarthy that it is necessary to look at these protocols on a case-by-case basis in order to weigh the benefit/risk ratios. Ms. King agreed with Dr. Juengst that the RAC has to tackle the difficult problem of making a distinction between correction and enhancement in gene transfer protocols. Ms. King stated that the risks to normal subjects are justified only in terms of the overall benefit to the society. This same statement is applicable to studies involving patient subjects since most of the gene transfer protocols proposed to date are Phase I studies that at the present are not going to benefit patients directly. Unfortunately, the way that gene therapy research has been presented to the public generates misconception among the public that the treatments are beneficial to the patient subjects. The RAC should provide the public with an informed assessment of the field.

Dr. Aguilar-Cordova thanked the *ad hoc* ethics consultants for providing the RAC with a wealth of information regarding the general aspects of normal subjects in medical research. He asked the RAC and the *ad hoc* experts to address the issue more specifically from the gene therapy perspectives.

VII-B. Gene Transfer Research - Use of Normal Subjects

Dr. McCarthy suggested that the RAC should form a subcommittee or the newly proposed Gene Therapy Policy Conference (GTPC) should be used as a forum to address the policy issue of enhancement gene transfer research. It is timely to revisit Appendix M, the *Points to Consider*. Dr. McCarthy highlighted the fact that gene therapy has the potential of permanently altering a subject's genetic structure, and for this reason, has special concerns that are different from other clinical applications involving pharmaceutical drug development. There is an urgency of "getting it right the first time" for gene transfer research. Enhancement intervention is associated largely with social consequences. The reproductive concerns are much greater for normal healthy subjects than for terminally ill subjects. The RAC should be proactive in developing policy relevant to potential germ line applications. Furthermore, gene therapy carries a mystique for the lay public that is not associated with any other form of medical research, namely, notions of remaking the human race. Dr. McCarthy noted the importance of creating policy that sets limits and normalizes the types of feasible interventions. Such policy is critical in order to prevent a public perception that genetic scientists are "playing God."

Dr. Juengst agreed with Dr. McCarthy that three issues distinguish gene transfer studies from other kind of clinical research: (1) the permanency of the biohazards, (2) the potential risk of germ line integration, and (3) its high public visibility.

Dr. Markert disagreed with statements that gene transfer research is unique from other types of medical research. She stated that for some pediatric disorders, the effect of bone marrow transplantation is not readily reversible. With regard to safety, gene transfer has so far been shown to be quite safe; there is no incidence of adverse effects, e.g.,insertional mutagenesis. By contrast, the first large number of patients who received the bone marrow transplant did not do well; it was the later trials that finally proved the procedure to be useful.

VII-C. Gene Transfer Research - Enhancement

Dr. Saha asked Dr. Juengst how one would go about defining the line for enhancement interventions; human populations are not genetically homogeneous. Another puzzling issue is how to separate the health goal from the social goal. Dr. Saha used dwarfism as an example. Should treating such an inherited condition with gene transfer to be considered as addressing a social goal or a health goal? In the case of dwarfism, Dr. Saha said that he would have no reservations about treating dwarfism with growth hormone. Dr. Juengst responded that normal attributes are defined statistically and theoretically by a bell curve. In practice, it is relied on collection of data on each trait to define a "normal" range for policy purposes. As to the question of distinction between social and health goals, Dr. Juengst said that the distinction is made in an arbitrary, yet understandable way. For people with short stature with no medical problem, it is simply a matter of trying to improve social standing within the normal range. Dr. McCarthy noted that there is no clear defining line for socially acceptable norm. The "norm" is accepted by a consensus opinion, and it could change over time.

Dr. Ross noted that genetic enhancement is not necessary to enhance capabilities beyond the normal range; it could be improvement within the normal range, e.g., getting thinner, more hair, taller, or smarter. With regard to the RAC preference of using the seriously ill patients as experimental subjects for gene therapy, Dr. Ross stated that the RAC should start to consider incorporating patients who are mildly to moderately ill in order to obtain more scientific information from the gene therapy studies. Dr.Juengst agreed that this subject required more deliberation. There are two rationales for using terminally ill patients for gene transfer studies: (1) they have the most desperate need for benefit, and (2) they are less likely to suffer from any serious adverse effects, e.g., germ line alteration. One significant drawback to using terminally ill subjects in clinical research is the likelihood that most of these subjects cannot provide true informed consent due to their vulnerability. Normal volunteers are more likely to give a true informed consent.

Dr. McIvor inquired about the major ethical concerns related to gene transfer for cosmetic purposes, e.g., to improve skin complexion or prevent baldness. Dr. Aguilar-Cordova inquired how cosmetic gene transfer differs from other cosmetic applications, e.g., plastic surgery is difficult to reverse; in terms of germ line risk, gene transfer vectors such as plasmid DNA or recombinant adenovirus pose little risk to the germ line. Dr. Juengst responded that cosmetic improvements for the purpose of gaining an unfair advantage in social competition poses a moral problem that it is not unique to gene therapy. Dr.Saha noted that gene transfer for baldness prevention would "level the playing field" of social competition.

Dr. Mickelson noted that the RAC has traditionally considered gene therapy protocols in the context of treatment for medically recognized problems. Outside of this context, there are a variety of value judgments that could be made depending on numerous safety, social, and ethical considerations.

Dr. Lysaught noted that the RAC functions in a stewardship model to foster social good. In the past 6 years, all the protocols that have come to the attention of the RAC are for treating patients with serious or in some cases milder medical conditions. The use of normal subjects in Dr. Crystal's protocol represents a leap in the criteria of subject selection. Dr. Mickelson agreed that using normal subjects poses a major

shift that warrants ethical consideration.

Dr. McIvor noted a protocol for treating mild Hunter's syndrome (#9409-087) by Dr. Chester Whitley from the University of Minnesota. The patient treated under this protocol has the inherited monogenic disease but is leading a relatively normal life. Dr. McIvor emphasized that the primary concern of the gene transfer study is not to worsen the subject's medical condition; the same consideration is applicable to normal subjects. Dr. Aguilar-Cordova added that Dr. Mark Batshaw's ornithine transcarbamylase protocol (#9512-139) similarly belongs to this category of patients with genetic diseases, i.e., leading relatively normal lives.

Dr. McCarthy noted that the issue of gene transfer for the purpose of cosmetic intervention is a subject of considerable ethical debate. He noted that from his expertise of participating in ethical debate on this subject at the Kennedy Institute, Georgetown University, there is far from any consensus among ethics colleagues over this issue. People who place higher emphasis on social value are less supportive of intervention for cosmetic purposes. Treating baldness, correcting minor facial distortions, or skin blemishes do not make much difference to the society as a whole. On the other hand, people who value individual autonomy favor those decisions to be made by the individuals. Only the individuals can decide on the benefit of the cosmetic interventions for themselves. Dr. McCarthy said that no consensus has arisen from such ethical debates.

Responding to Dr. Lysaught's comment about the RAC as a stewardship model, Dr. Juengst emphasized that the goal of clinical research is always to obtain important knowledge that will benefit society as a whole (whether sick or healthy individuals), even though the subjects themselves will not directly benefit from the study.

Dr. Lysaught explained that at the present state-of-the-art, gene therapy has not been proven to be efficacious; it is more justifiable to use the technology on patients who have exhausted all alternative treatments than patients who have alternative treatments.

Dr. Aguilar-Cordova inquired whether it would be more justifiable to start with the highest possible dose in gene therapy trials involving serious diseases to determine any efficacy. Dr. Juengst responded that physicians are required to "first do no harm."

Ms. King responded that the risk versus benefit ratio must be weighed; nonmaleficence the guide rather than beneficence. Dr. Lysaught said that the investigator should strive to minimize the risk and to maximize the benefit through good scientific design of the protocol. Dr. McCarthy stated that the study should be conducted to obtain generalizable medical knowledge not just for treating a particular patient; the study has to be conducted in a systemic fashion with increasing doses to obtain data that will establish the medical knowledge.

Dr. Aguilar-Cordova suggested that a GTPC should be held to expand discussion of this topic. Dr. Ross asked the FDA representatives if they were aware of any cosmetic gene transfer applications that may be proposed in the near future. Dr. Miller (FDA) responded that she was unaware of any such proposals under consideration, but encouraged the RAC to initiate these timely ethical discussions well in advance of such applications. Dr. Lysaught inquired as to how the FDA would respond to a cosmetic enhancement protocol if one were submitted today. Dr. Miller responded that the FDA would consider the risk versus benefit ratio of such a proposal and make its decision on that issue. For ethical considerations, the FDA would defer to the RAC. Dr. Saha inquired whether the FDA would recommend RAC review of such a protocol, e.g., cosmetic enhancement, regardless of any ties to NIH funding. Dr. Miller said that the FDA would encourage the sponsor to voluntarily submit such a protocol to the RAC.

Dr. Saha sensed an urgency for the RAC to deliberate on the enhancement issue. He said he is not personally against enhancement, but the RAC needs to formulate a guideline to balance the societal acceptability versus the individual need. Dr. Aguilar-Cordova asked Dr. Saha to propose to formalize his comments in the form of a motion to convene aGTPC on this issue.

Dr. Saha made a motion to convene the firstGTPC on the issue of enhancement gene transfer protocols in anticipation of submission of such protocols to the RAC. Dr. Mickelson seconded the motion.

Drs. Wolff and Lysaught made a friendly amendment to include a discussion of the use of normal subjects in gene transfer studies, and to amend Appendix M,*Points to Consider* regarding this issue. Dr. Saha accepted the friendly amendment.

Dr. Markert said that a general discussion without a specific protocol may not be able to address the issue when a protocol is submitted. For a historical perspective, Ms.Knorr invited Dr. Anderson to comment on the necessity for an actual protocol submission at the time the*Points to Consider* were originally drafted. Dr. Anderson responded that the Working Group on Human Gene Therapy established by the RAC drafted the *Points to Consider* in 1986; the basic points of this document have remained essentially unchanged to date. He encouraged the RAC to convene the firstGTPC to discuss the enhancement issue, stating that it will provide a framework for guidance in reviewing the first enhancement gene transfer protocol.

Dr. Ross inquired how such a GTPC should be structured. Dr. Aguilar-Cordova said that a panel of experts would discuss the issue and the second day the RAC could consider the GTPC recommendations for the purpose of amending the*NIH Guidelines*.

Dr. Juengst suggested that enhancement and normal subjects should be separate topics.Dr.Saha agreed. Dr. Ross noted that normal subjects might potentially be used as a control group to study gene therapy, and there is a need to address this issue. Dr.Lysaught sensed the urgency of enhancement gene transfer policy that needs to be addressed first. Dr. Aguilar-Cordova noted that these two issues are closely related, and they are preferably discussed at the same meeting. Dr.Saha said that each issue needs in depth discussion, and he would let ORDA decide on the format. Dr.Lysaught said that a RAC meeting should follow up on the recommendations made by GTPC to amend the *NIH Guidelines*.

Committee Motion 6

A motion was made by Dr. Saha and seconded by Dr. Mickelson to convene a GTPC to discuss scientific and ethical issues involving the inclusion of normal human subjects in gene transfer studies designed to answer basic biological questions that will facilitate scientific progress of therapeutic trials versus enhancement gene transfer protocols. The motion passed by a vote of 8 in favor, 0 opposed, and no abstentions.

VIII. DISCUSSION REGARDING PROPOSED ACTIONS TO THE *NIH GUIDELINES* -- NIH OVERSIGHT OF HUMAN GENE TRANSFER RESEARCH/ KNORR

Overview--Ms. Knorr

The RAC continued its discussion of the *Proposed Actions* to revise the *NIH Guidelines* regarding NIH oversight of human gene transfer research. Ms.Knorr summarized the history of the*Proposed Actions.* On July 8, 1996, the NIH Director published a *Notice of Intent to Propose Amendments to the NIH Guidelines*

for Research Involving Recombinant DNA Molecules Regarding Enhanced Oversight of Recombinant DNA Activities (61 FR 35774). The NIH Director proposed in this *Notice of Intent*: (1) elimination of the RAC and establishment of the ORDA Advisory Committee to ensure public accountability for recombinant DNA research and relevant data, (2) implementation of GTPC to augment the quality and efficiency of public discussion of the scientific merit and the ethical issues relevant to gene therapy clinical trials, and (3) continuation of the publicly available, comprehensive NIH database of human gene transfer clinical trials, including adverse event reporting. NIH received 71 written responses to the *Notice of Intent*; the overwhelming majority of the responses favored retention of the RAC due to its historical importance. On November 22, 1996, the NIH Director published a *Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules* (61 FR 59725). These *Proposed Actions* were in response to public opinion and in keeping with the NIH Director's intent to increase the usefulness and productivity of public discussion of gene therapy. In the November 22, 1996,*Proposed Actions*, the NIH Director proposed to: (1) retain the RAC, while modifying its roles and responsibilities relevant to human gene therapy research, (2) continue RAC discussion of novel human gene transfer experiments without RAC approval of individual human gene transfer experiments, (3) reduce the membership of RAC from 25 members to 15 members, (4) regularly conveneGTPCs, and (5) maintain public access to human gene transfer clinical trial information. At its December 9, 1996, meeting, the RAC discussed and accepted the overall concepts in the *Proposed Actions*, however, a motion was made to table forwarding the RAC'srecommendation to the NIH Director until the committee completed its recommendations on several minor issues at the March 1997 meeting. A significant issue requiring RAC's discussion was to define the role of the RAC relative to the proposed GTPC.

Dr. Ross said that an issue to be addressed by the RAC is the timing of investigator's submission to the RAC versus submission to FDA; the RAC is receiving protocols after FDA approval. Ms. Knorr said that this issue will be addressed in the later session of NIH/FDA strategy to streamline the review procedure. Dr. Lysaught noted that the RAC will discuss a protocol, but it will no longer give approval. Approval is an important endpoint of such a RAC discussion.

The RAC/GTPC Relationship

Dr. Aguilar-Cordova noted that the relationship between the RAC and GTPC should be the first item of discussion. The November 22, 1996, *Proposed Actions*, envisioned GTPCs as entities independent of the RAC. Several RAC members expressed their opinion that the GTPC should be closely linked to the RAC, perhaps convening the GTPC the first day of a scheduled RAC meeting. In doing so, the RAC could perform an active role in establishing the GTPC agendas. Dr. Saha inquired if the RAC's recommendation that GTPC should be closely tied to the RAC would be contrary to Dr. Varmus' intention. Ms. Knorr responded that as an advisory body to theNIH Director, any such recommendation would be considered. The NIH Director can accept, reject, or modify the recommendation.

Dr. Lysaught said that the issue of RAC review of the Informed Consent document should be discussed. Dr. Ross inquired if Appendix M, the *Points to Consider*, will continue to be addressed by the investigators. Ms. Knorr responded that no changes have been proposed with regard to the submission requirement; therefore, submission of Appendix M will still be required.

Dr. Aguilar-Cordova asked the RAC if they were ready to propose a motion regarding theGTPC issue. Dr. Mickelson stated that she favored a close relationship between the RAC and GTPC. Dr. Ross proposed that one member of the RAC should co-chair each GTPC and assist in establishing the conference agenda; when appropriate, the GTPC should be held the first day of a scheduled RAC meeting, and the RAC co-chair will report to the RAC regarding the GTPC recommendations. Dr. Aguilar-Cordova suggested the following friendly amendment to the motion. If aGTPC is convened outside the regularly

scheduled RAC meetings, the RAC members should be invited to participate. Dr. Ross accepted the friendly amendment. Ms. Knorr noted that the NIH Director would weigh heavily the RAC's recommendation on GTPC topics; however, the NIH Director has the final authority to convene and choose GTPC topics. Dr. Ross noted that investigators, industry, public, and the FDA may make recommendations for GTPC topics. Dr. McIvor inquired as to the source of funding for GTPCs. Ms. Knorr responded that NIH would be the principal source of funding for GTPCs; perhaps a more efficient use of resources is the suggested plan of holding GTPC in conjunction with RAC meetings. Dr. Lysaught inquired as to the format for these conferences. Dr. Aguilar-Cordova and Ms. Knorr responded that these conferences will be open to the public and will involvediscussion among a group of experts on a specific topic. The details of these conferences remain to be established.

Committee Motion 7

A motion was made by Dr. Ross and seconded by Dr. Markert to include the following modifications with regard to the role of the RAC relative to GTPCs: (1) one member of the RAC will co-chair each GTPC, (2) GTPCs will be held in conjunction with RAC meetings when appropriate (probably on the first day), and (3) all RAC members will be invited to attend GTPCs. The motion passed by a vote of 8 in favor, 0 opposed, and no abstentions.

Discussion Regarding Novel Protocols

Dr. Lysaught stated that the *Proposed Actions* call for the RAC to continue discussion but without *approval* of novel human gene transfer protocols. Dr. Lysaught noted that the RAC has endorsed Dr. Varmus' proposal to relinquish NIH approval of individual protocols; the next issue that the RAC should debate is the discussion of the novel protocols and defining the endpoint of these discussions.

Dr. McIvor inquired about the process that will be used in determining if a protocol is novel and thus requires RAC review. He noted the fact that RAC members do not review protocols in their entirety. Ms. Knorr responded that previously the RAC was overwhelmed by having to review each submission in its entirety. In response to the RAC's dilemma, ORDA has simplified the process by providing RAC members with a comprehensive summary of each submission with special emphasis on providing a detailed comparison to protocols previously registered with ORDA. Dr. Aguilar-Cordova noted that the summary information prepared by ORDA, including the comparison chart, should provide adequate information for prescreening a protocol regarding its novelty. Any RAC member wanting to review additional submission material can request that ORDA forward the relevant information. In response to Dr. McIvor's question about the process of RAC review, Ms. Knorr noted that in the November 22, 1996, *Proposed Actions*, full RAC review would be determined by a majority of RAC members. At the December 1996 RAC meeting, several RAC members were concerned that a minority concern, i.e., public members, would not trigger RAC review. Consequently, the RAC changed the number of votes required to trigger full review to a minimum of 3 RAC members. In this 3 month period since the December 1996 RAC meeting, ORDA has received a total of 10 protocols; one protocol (#9701-171) was recommended for full RAC discussion.

As to the prescreening process for full RAC discussion, Dr. McIvor preferred to have 3 RAC members review the entire protocol to make the recommendation for full RAC discussion. Dr. Saha and Ms. Knorr noted that a consensus opinion regarding the necessity of full RAC review is readily obtained by circulating the summary information among all the RAC members to allow a decision to be made within the turning around time of 15 working days. Dr. McIvor was concerned that no one reads the entire protocols submitted by the investigators. Ms. Knorr explained that each protocol is reviewed by the ORDA staff, and the summary information is prepared for the RAC. Dr. Saha noted that such a summary cover sheetprovides adequate comparative information for the RAC to determine its novelty; ORDA draws on its

institutional memory to prepare the cover sheet summary.

Informed Consent Document

Dr. Ross raised the issue of reviewing the Informed Consent document submitted with each protocol. IRBs have the responsibility for approving of the Informed Consent document. But from her experience of reviewing such documents, Dr. Ross found that many Informed Consent documents have not adequately responded to Appendix M, the *Points to Consider*. She asked if a RAC subcommittee should be charged with the responsibility of reviewing the Informed Consent documents. Alternatively, Ms. Knorr suggested to provide IRBs with relevant guidance through Appendix M, the *Points to Consider*, to ensure that RAC requirements are met. Such guidance may be provided through the Office for Protection from Research Risks (OPRR). Dr. Saha noted that the RAC reviews only the novel protocols and the Informed Consent documents of those protocols; other Informed Consent documents of exempt protocols are not within the purview of the RAC. Drs. Aguilar-Cordova and Markert agreed that the RAC could set the policy through the *NIH Guidelines* but not necessarily review each Informed Consent document. Drs. Lysaught and Ross were concerned about deficiency of most Informed Consent documents.

Dr. Markert proposed a motion to have ORDA provide the most recent version of Appendix M, the *Points to Consider*, to the Chairs of IRBs, and identify to them pertinent changes of the *NIH Guidelines* regarding RAC oversight of human gene transfer protocols particularly with regard to the Informed Consent documents. Dr. Saha seconded the motion.

Committee Motion 8

A motion was made by Dr. Markert and seconded by Dr. Saha to recommend that ORDA provide the most recent version of Appendix M, the *Points to Consider,* to the Chairs of IRBs. ORDA should identify pertinent changes of the *NIH Guidelines*. The motion passed by a vote of 8 in favor, 0 opposed, and no abstentions.

Dr. Lysaught was concerned about the IRB's failure to enforce compliance under the *NIH Guidelines* regarding the Informed Consent documents. Dr. Wivel stated that IRBs are under the oversight of OPRR, and OPRR has the responsibility to ensure that IRBs comply with all Federal regulations.

Issue of IBC Approval

Dr. Aguilar-Cordova called on the RAC to address the issue of IBC approval stated in the proposed amendment to the Section III-C-1 of the *NIH Guidelines*. This proposed section requires the investigators to obtain IBC approvals from: (1) any institution involved in the production of the vectors for human applications, (2) any institution at which there is *ex vivo* transduction of the recombinant DNA material into target cells for human application, and (3) any institution at which the recombinant DNA material will be directly administered to humansubjects. Dr. Aguilar-Cordova suggested that IBC approval only should be required of any institution at which the recombinant DNA material will be directly administered to human subjects; it is not necessary to ask the IBC of the vector production laboratory to review all protocols that use the vectors produced by the facility. Ms. Knorr explained that the *NIH Guidelines* does not specify which institution involved in the gene transfer protocol requires IBC approval.

Dr. Ross stated that it is not appropriate to require a vector production site to obtain IBC approval for protocols that will be conducted at other sites. Dr. Aguilar-Cordova said that the IBC of the vector production site will provide oversight regarding the safety issue of vector production according to the *NIH Guidelines,* but it will not review clinical protocols that are not performed at that particular site. Dr. McIvor

agreed. Drs. Lysaught and Mickelson were concerned that the vector production site will have no feedback from clinical trial sites that use the vectors. Dr. Aguilar-Cordova said that FDA has the authority to ensure that vectors are produced according to Federal regulations. Dr.Saha noted that in an analogous situation, it is difficult to require a pharmaceutical company to be responsible for all physicians prescribing their drugs to the patients.

Dr. Aguilar-Cordova suggested deleting the IBC approval requirement from the vector production site for those protocols to be conducted at other clinical sites. Dr. McIvor noted that the proposed Section III-C-1 similarly requires IRB approvals from all institutions involved with human gene transfer protocols. Ms. Knorr said that the IRB and IBC requirements have to be separated; only the clinical sites require the IRB approvals.

Dr. Markert suggests a sentence to read, "Prior to submission of a human gene transfer experiment to the NIH/ORDA, the principal investigator must obtain Institutional Biosafety Committee approval and Institutional Review Board approval from each institution in which human subjects will undergo gene transfer, specifically, the principal investigator must obtain Institutional Biosafety Committee approval from ..."

Dr. Lysaught was concerned that an investigator would be able to obtain a vector from a vector production laboratory and conduct a human gene transfer experiment in another country.

Ms. Bridget Binko, Cell Genesys, stated that the requirements of IBC approval from any institution at which there is *ex vivo* transduction of recombinant DNA material into target cells for human applications should be removed since it could be a contract laboratory performing the *ex vivo* transduction procedure for a clinical investigator. Drs. Markert, Saha, and Aguilar-Cordova agreed.

As a point of clarification, Ms. Knorr stated that *NIH Guidelines* applies to all NIH-funded investigators and institutions; commercial facilities if collaborating with NIH-funded investigators or institution are covered under the *NIH Guidelines*.

Dr. Ross suggested a sentence to read, "Prior to submission of a human gene transfer experiment to NIH/ORDA, the principal investigator must obtain IBC and IRB approvals from each institution that will administer a recombinant DNA material to human subjects." Drs. Markert and Saha agreed to the statement.

Committee Motion 9

A motion was made by Dr. Ross and seconded by Dr. Saha to modify the approval requirements of IBCs involved with human gene transfer protocols under Section III-C-1 of the *NIH Guidelines*. Two proposed IBC approval requirements are to be removed: (1) any institution involved in the production of the vectors for human application, and (2) any institution at which there is *ex vivo* transduction of the recombinant DNA material into target cells for human application. The RAC proposed that IBC approval shall be obtained from each institution at which the recombinant DNA material will be directly administered to human subjects. The motion passed by a vote of 6 in favor, 0 opposed, and 2 abstentions.

Dr. Mickelson abstained and stated that she was not comfortable with the removal of the IBC oversight from vector production and *ex vivo* transduction sites. Some cross reference should be made to other sections of the *NIH Guidelines* pertaining to the safe conduct of the recombinant DNA material for human use. Dr. Mickelson said that she prefers to retain IBC approval of the facility performing *ex vivo* transduction of human target cells. As a point of clarification, Ms.Knorr said that removal of IBC approval

from Appendix M does not remove IBC oversight of the facilities from other sections of the *NIH Guidelines,* i.e., Appendix G, *Physical Containment*, and Appendix K, *Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules*.

Dr. Lysaught abstained and stated that she was uncomfortable with the reduction of IBC oversight.

Dr. Miller stated that from the FDA perspective, the sponsor is the key person who has the legal responsibility for oversight of the entire process from production to administration to the patients. FDA closely monitors vector production, cell >

Transfer interrupted!

very step of the process. She agreed that the IBC of the vector production site should oversee the vector production issue rather than reviewing the clinical protocol. Similarly, the *ex vivo* transduction could occur at a facility independent of the clinical application site.

Additional Issues

Ms. Knorr noted that the present *Proposed Actions* published on February 14, 1997, removed the requirement of simultaneous submission of Appendix M to FDA in response to Dr. Miller's letter of November 20, 1996. Such a submission is required under the present NIH/FDA consolidated review plan. Dr. Aguilar-Cordova said that the RAC can address this issue in the NIH/FDA streamlining session later on in the meeting. Dr. Markert said that the RAC should address the issue raised by Steven Kradjian of Vical Inc., in his letter of January 7, 1997. Mr. Kradjian suggested removing the requirement of prior IBC and IRB approvals before a protocol is submitted to NIH/ORDA. Mr. Kradjian stated that this requirement significantly delays initiation of a protocol. Dr. Aguilar-Cordova said that the RAC will takeup this issue later on in the meeting.

IX. UPDATE ON THE NIH HUMAN GENE THERAPY RELATIONAL DATABASE

Presentation: Theresa Pierson, NIH Consultant

Ms. Knorr introduced Ms. Pierson who has taken the task of developing the relational database of gene transfer protocols.

Presentation--Ms. Pierson

Ms. Pierson stated that since July 1996, the database has been developed in collaboration with NIH Division of Computer Research and Technology, ORDA staff, FDA staff, and in consultation with Drs. Gary Chase and Dusty Miller, former members of the RAC.

Ms. Pierson presented with overhead illustration the background, the scope, and the general design of the human gene transfer relational database. The database will capture the submission phase and the follow-up phase clinical trial information. The database will reside in an IBM Mainframe computer at the NIH Computer Center. It will feature dynamic tables with drop-down selection boxes for data entry and

query purposes. The end-user will access information through pre-defined query, as well as ad hoc query. The database will be developed in 3 phases: local database development, world wide web summary information, and world wide web query and reporting functionality.

The general design of the database will include a submission section containing information regarding protocol definition, contact information, approval information, clinical parameters, and gene transfer information. This information will be captured from the protocol submission material provided by the investigators in accordance with Appendix M-I, *Submission Requirements -- Human Gene Transfer Proposals*, of the *NIH Guidelines*. Included in the protocol definition are: NIH protocol number, FDA IND number, protocol title, NIH protocol status, NIH protocol status date, principal investigator, funding source, and protocol modifications. Contact information will list: clinical trial site; clinical trial site contact; industry sponsor; industry sponsor contact; IBC and its officer; chair and contact; IRB and its chair and contact; vector source; vector source contact; and vector production facility. The approval information will include: dates of cover letter, NIH receipt, IRB approval, IBC approval, RAC review, IND approval, and NIH approval/exemption. The clinical parameters will describe: the phase of the trial, trial application type, disease, concomitant medications, protocol goals and objectives, proposed patient accrual, treatment groups, dosing schedule, clinical inclusion and exclusion criteria, and patient age and gender. Gene transfer information will describe: the functional gene, marker gene, vector name, parental vector, regulatory elements for gene expression, vector type, production method, delivery method, *ex vivo* or *in vivo* target cells, and route of administration.

The follow-up section will ask the investigators to provide the follow-up information in accordance with Appendix M-VIII, *Reporting Requirements -- Human Gene Transfer Protocols*. These data include: brief narrative summaries relating to evidence of gene transfer, evidence of gene expression, evidence of biological activity, evidence of problems associated with gene transfer, persistence of transduced cells expected, persistence of transduced cells observed, immune responses, treatment groups, accomplished goals and objectives, adverse events, patient deaths, actual patient accrual, date of the first treatment, date of the most recent treatment, and detection of RCV. For replication-competent retroviruses (RCR), the investigators will be queried as to what assays are used, if production materials are tested, patient samples are tested, and the results of thetestings. In the adenovirus studies, investigators will be asked if replication-competent adenoviruses (RCA) are detected.

Only summary information will be requested as not to jeopardize publication of such data. This will not be a patient registry. Relevant publications will be cited for the purpose of identifying peer-reviewed published data.

Other Comments

Drs. Aguilar-Cordova and Mickelson noted that the database will capture a great detail of protocol information and some of them are in the submission materials. Dr. Aguilar-Cordova was concerned that investigators will be required to provide the complex information of the database. Ms.Knorr said that the RCV section was developed in consultation with the FDA staff; it is important information to be used by the FDA staff as well. The database is a major ORDA function and its staff will capture most of the information. In the future, NIH will coordinate with FDA to develop a consistent format of annual data reporting to capture the follow-up information. Efforts will be made to ease the burden upon the investigators.

Dr. Wolff noted that one objective of the follow-up section is documentation of the efficiency of gene transfer and evidence of gene expression. He agreed to assist ORDA staff to develop details of this section to capture and evaluate gene expression data. Ms.Knorr noted that the information is to help the

public to understand and to monitor the field of gene transfer studies.

X. DATA MANAGEMENT--FUTURE DIRECTIONS/SMITH

Dr. Aguilar-Cordova called on Dr. Smith to lead the discussion of the future directions of Data Management Subcommittee. Dr. Smith provided a brief history of the origin of Data Management Subcommittee. This function started 6 years ago when the late Dr.Brigid Leventhal, an pediatric oncologist at Johns Hopkins University, was serving with the RAC. Dr. Leventhal noted the needs: (1) to provide institutional memory of protocols reviewed by the RAC, (2) to serve as a

reference for RAC review of new protocols, (3) to provide public disclosure of gene transfer research information, and (4) to provide a guidance for future gene therapy development. As the number of gene transfer protocols and the number of accrued patients expanded, the Data Management Subcommittee has become a cottage industry supervised by 7 RAC members. Data reporting was started on a semiannual basis and later changed to an annual basis of reporting. Atthe beginning, the information captured was mostly demographic with emphasis on adverse events to gene transfer vectors. Later as the field developed, additional questions regarding gene expression and clinical efficacy of gene transfer were asked to the investigators. Dr. Smith emphasized that the database development is a dynamic process, the RAC needs to discuss what types of data should be collected. He preferred to have simple check off boxes and multiple choice format rather than a narrative format of Data Reporting Forms for the investigators to complete. Dr. Smith noted the real challenges of the database are to collect the increasing amount of clinical trial data, and at the same time, condense the information without imposing undue burden to the investigators. Another important task is to evaluate the collected data. Dr. Smith noted that Data Management Subcommittee is a major undertaking for both the RAC and theORDA staff.

Other Comments

Ms. Knorr stated that the overwhelming majority of comments received byNIH in response to July 8, 1996, *Notice of Intent*, were in support of data management. Dr.Varmus is committed to maintain data management for the purpose of public awareness of theNIH mission, and for helping NIH to identify the gaps in the area of gene therapy research.

Dr. Aguilar-Cordova inquired as to how the Data Management Subcommittee has been conducted in the past. Dr. Smith responded that the last major review of the data on gene transfer studies was conducted a the June 1995 RAC meeting; the essential elements of that Data Reporting Form are very similar to what is currently proposed.

Dr. Saha said that a useful format would be to present the information in a format currently used in the summary cover sheet for RAC members to identify novel protocols for RAC review. As to the format, Ms. Knorr noted that in the first phase of the database development, there is no user query function, and the data will be summarized in defined reports covering specific areas.

Dr. Ross stated that in the long term, the database should be an on-line database; she asked how the information will be entered into the database. Ms. Knorr responded that protocol information will be extracted from the submission documents, and the follow-up information will be supplied by the investigators. The RAC has previously indicated that investigator-supplied information needs to be interpreted by the RAC or its subcommittee, and the reviewed materials will be entered into the database. Dr. Ross said that from her experience of reviewing the Data Reporting Forms in the past, she found the areas of evidence of gene transfer, gene expression, and biological activity to be the most difficult to interpret; the questionnaire should be improved in order to obtain interpretable information. In addition,

concomitant treatments or medications should be described in order to evaluate any effects attributable to gene transfer. Dr. Ross said that most of the information is already in the submission materials, and the data reporting should not be an onerous burden to the investigators. Ms.Knorr noted that Dr. Wolff has offered to assist in developing the questionnaire regarding evidence of gene transfer.

Dr. McIvor stated that the database proposal is very thorough, and it will provide useful information. He was concerned that the Data Reporting Form might appear cumbersome to the investigators. Dr. Aguilar-Cordova was concerned that the investigators will be required tocomplete different reporting forms for different agencies, i.e., FDA,IRB, and IBC in addition to the RAC. Dr. McIvor noted that the investigators might have variable standards as to the interpretation of evidence of gene transfer and efficacy of gene therapy. Dr. Wolff said that specific details should be provided in the questionnaire as to exactly the level of protein expressed, the method of measurements, and exact biological effect. Dr. Aguilar-Cordova noted that the quality not just the quantity of data captured are important. MsKnorr noted that the proposal is a starting point; the suggestions are useful.

Dr. Markert recognized that the database is to provide an institutional memory of protocols submitted to the RAC. She was concerned about the complexity of the Data Reporting Form; it will be an onerous burden to the investigators, and it is duplicative of FDA's reporting requirements. Dr. Markert preferred a narrative form of the database that summarizes each protocol.

Dr. McIvor was concerned that detailed data of a study made public in an on-line database might become an impingement of the publishability of such data in a scientific journal. Dr. Aguilar-Cordova noted that it will raise a proprietary issue for companies as well.

Dr. Smith responded to several issues raised by RAC members. With regard to the adverse events report, the investigators usually submit a copy of the report they send to FDA; it should not be a burden for the investigators. The RAC needs to keep a broader perspective of the adverse effects such as the cerebral edema observed in the brain tumor protocols of treating patients with the vector producer cells (VPC). Such information is useful in the evaluation of new proposals using the same approach. With regard to the efficacy question, Dr. Smith agreed that it is not an easy task to define criteria to evaluate gene expression and treatment efficacy; there is a balance between too much and too little specification of the Data Reporting Form.

Dr. Aguilar-Cordova stated that there is a huge public support for the database in order to keep the public informed about the state of the art of the field of gene therapy; the discussion of the database should serve as a good starting point for this task.

Dr. Markert emphasized that the database should not compromise the investigators' ability to publish their data in scientific journals.

Ms. Knorr noted that one purpose of the database is to provide the public with information to ease their fear of this new technology; as an example, she mentioned the RAC discussion of the adverse events of the brain tumor protocols in which the investigators explained to the public that these adverse effects were not directly related to the gene transfer procedure.

Responding to Dr. Markert's concern about publishability, Dr. Smith said that in the past, the RAC did not ask the investigators to provide the actual data of the study, and it did not impinge on thepublishability of those data. In the June 1995 Data Management, 7 members of the Data Management Subcommittee reviewed the submitted data in different disease categories. Ms.Knorr drew attention to the status report and scientific report that summarized the data collected at the June 1995 Data Management.

Dr. Markert preferred to collect the published data rather than data of studies in progress. She felt that adverse events should be reported immediately.

Dr. McIvor recalled that when Dr. Leventhal started Data Management, there were many gene marking protocols to be reviewed by the RAC, but there were very few published data. For this reason, Dr. Leventhal proposed having data management. Dr. McIvor implored the RAC to identify the purpose of the database in order to focus its development.

Goals and Purposes of the Database

Dr. Aguilar-Cordova called on the RAC to articulate the goals of data management. One goal already mentioned is to maintain the institutional memory. Dr. Markert said that another purpose is to provide administrative details of protocol registration, e.g., contact information.

Dr. Ross mentioned one of the major function is to assess progress in gene therapy research, i.e., to identify areas of promise and overpromise, and any gaps in the development of the field. Another purpose is to provide public access to gene transfer protocol information. Dr. Markert was concerned that pre-publication materials may not have adequate quality control by peer review. Dr. Aguilar-Cordova stated that such an assessment of the field could be accomplished by reviewing the published information and making such information understandable and accessible to the public.

Dr. Aguilar-Cordova noted that another purpose is to make scientific risk assessment of gene transfer protocols. Dr. Lysaught agreed.

Dr. Lysaught noted that at the beginning of the Data Management Subcommittee, there were very few published papers, and the public was uncertain of the status of the field. Ms. Knorr agreed that public information was a need at that time.

Dr. Smith made a remark that the success of the database will depend on the cooperation of the investigators. If an investigator considers information worthy of putting in the database, it should be welcome; if the information is considered not worthy of publication, there is no use to include the information in the database.

Dr. Aguilar-Cordova suggested coordinating with the FDA for the annual data reporting; FDA information is confidential, and the RAC database is in the public domain. Drs. Wolff and Markert were concerned that potentially the database could expand beyond the scope of what the ORDA staff and the RAC could cope with. Dr. Ross responded that the database development is an evolving process, and it will adapt to the practicality in the future. Dr. Markert emphasized that the investigators should not be put in a situation where data reporting becomes an onerous burden.

Ms. Knorr suggested that a subcommittee should be formed to work out the details of data management. Dr. Smith noted several issues to be addressed for the long term: (1) Annual review function. These questions include: how the data will be collected for the annual review? Who will be responsible for entering the data, i.e., investigators versus ORDA staff? How the data are to be reviewed, full RAC versus a subcommittee? (2) Ongoing data review. As adverse reports come in on a continual basis, who will review them? Will the database be updated continually and will the public and the investigators have access to such adverse effects reports? Dr. Smith stated that the RAC has an obligation to collect data for the June 1997 Data Management; this short term goal is a limited version of the status report of gene transfer protocols including elements of number of protocols, subcategories, and general question on

toxicity and efficacy to the investigators.

Dr. Aguilar-Cordova called on Dr. Markert to summarize the goals of the database. Dr. Markert stated that the goals are: (1) institutional memory, (2) administrative details, (3) assessment of the scientific progress, and (4) risk assessment. Dr. Lysaught stated that the fifth goal should be to provide public access to gene transfer protocol information and to dispel misunderstanding of gene therapy. Ms. Knorr noted that negative data is important to minimize any hype of gene therapy research.

Mr. Kradjian stated that gene therapy has progressed to the stage of product development; several protocols have advanced beyond the Phase I feasibility studies. The RAC should be sensitive to the proprietary issue of product development. The purpose of the database should have a much more narrow focus limited to providing a registry of the protocols and providing safety or risk assessment information, i.e, adverse events reporting. Serious adverse events should be defined according to FDA's definition for investigational products. Mr. Kradjian was concerned about disclosure of detailed protocol data regarding efficacy of products; such information should be obtained from the published papers of completed clinical studies. Premature disclosure of data can compromise the developmental process of new candidate products.

Dr. Glorioso noted that premature disclosure of information is an industry concern. Dr. Aguilar-Cordova said that published information should be acceptable. Dr. Markert clarified that the purpose to assess scientific progress may be accomplished by a simple summary statement. Ms. Knorr asked Mr. Kradjian to elaborate on what he would consider premature disclosure. Mr. Kradjian explained that he was not concerned about disclosure of most information of the Phase I studies, i.e., the initial application of a new technology. Industry is concerned about releasing information in the later stages of protocol development for a product that has been evaluated in the early stages; virtually any detail regarding the product's function and its potential efficacy at the biological or clinical levels are of concern. Mr. Kradjian said that it is acceptable to include only the published data.

Dr. Victoria Allgood (GeneMedicine, Inc.) was concerned about the stated goal of scientific progress. The sponsor and the investigators may view their project's scientific progress differently from the RAC's view. Negative data from the Phase I trial may provide insight for further development of the products. Dr. Lysaught said that this goal should be redefined. Dr. Mickelson suggested restating the goal to provide annual status reports of protocols. Dr. Glorioso stated that the RAC's goal is not to evaluate the product development; the RAC is to provide annual summaries of protocols and to identify safety problems as they arise.

Dr. Lysaught was concerned about the results of many gene transfer studies that are not published. Dr. Aguilar-Cordova said that the RAC should not attempt to preempt scientific publication of gene transfer studies. Dr. McIvor emphasized the importance of institutional memory for the RAC to identify novel protocols.

Dr. Markert proposed a motion to identify five goals of the database: (1) institutional memory, (2) administrative details, (3) annual status reports, (4) risk assessment, and (5) lay access to the gene transfer information. Dr. Wolff seconded the motion.

Committee Motion 10

A motion was made by Dr. Markert and seconded by Dr. Wolff to identify five goals of the gene transfer relational database as follows: (1) to maintain an institutional memory, (2) to provide administrative details of protocol registration, (3) to provide annual status reports of protocols, (4) to make risk assessment of

gene transfer protocols, and (5) to provide public access to the gene transfer protocol information. The motion passed by a vote of 7 in favor, 0 opposed, and 1 abstention.

Subcommittees

Dr. Aguilar-Cordova asked the RAC to focus on the forthcoming June 1997 data management. Ms.Knorr noted that at present, the IBM mainframe computer facility is not yet available for data management; the data to be collected for more than 170 protocols is beyond the capacity of the word processing program on a personal computer.

Dr. Ross suggested forming an interim June 1997 Data Management Subcommittee to work out the details regarding the data to be collected for June 1997 RAC meeting. Drs. Wolff andLysaught agreed to participate in the subcommittee to be chaired by Dr. Ross.

With regard to the long-term issues of the database, Dr. Aguilar-Cordova said a Data Management Subcommittee should address these issues. As a point of reference, he cited the FDA regulation, 21CFR 312.33, Annual Report. Ms. Knorr stated that the subcommittee needs to address the issues in a timely fashion to coordinate the database development with the NIH Division of Computer Research and Technology. Sections of the developed database program that raise concern can be blocked. All the RAC members present including Drs. Ross, Wolff, Lysaught, Mickelson, Aguilar-Cordova, Markert, Saha, McIvor, and Glorioso agreed to participate in the Database Subcommittee.

Dr. Smith inquired if the RAC should publish a summary report evaluating the field of gene transfer research on an annual basis. Dr. Aguilar-Cordova responded that such a report is useful and can be published in professional journals.

XI. DISCUSSION REGARDING REGISTRATION OF PHASE III CLINICAL TRIALS/KNORR

Ms. Knorr made a reference to the FDA regulation, 21CFR 312.21, regarding definition of Phases of a clinical investigation. She asked the RAC to comment on whether the RAC should consider an amendment to the *NIH Guidelines* regarding the submission and reportingrequirements of Phase III gene transfer trials. According to the FDA definition, Phase III studies are performed after preliminary evidence suggesting effectiveness of the drug has been obtained. They are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Ms.Knorr noted that there are issues of proprietary information and product development in the later stages of gene transfer protocols. She inquired if the amendment should include Phase II studies.

Dr. Aguilar-Cordova noted that Mr. Kradjian suggested that the adverse effects of these later stages of development be reported to the RAC, and only published citations be captured by data management. Dr. Markert stated that Phase III should be exempt from the registration requirement, and the RAC should discuss if Phase II should be similarly exempted.

Dr. Ross noted the ambiguity of Phase II definition; many protocols have been labeled as Phase I/II studies by the investigators and sponsors. Dr. Andra Miller stated that from the FDA perspective, those studies are all considered as Phase I. 21 CFR 312.21 defines Phase I and Phase II studies. Phase I trials are: (1) to ensure or to determine safety of a particular drug, and (2) to determine metabolism and pharmacologic actions, side effects with increasing doses. Phase I studies usually involve small number of patients. By the end of Phase I, the investigators should be able to have enough information to define safe dosage and to advance to Phase II. In Phase II, the efficacy of a drug will be evaluated in a small

number of patients. Regarding Phase I/II labeling, Dr. Glorioso explained that part of the reason for the confusion is that some gene therapy studies involving rare genetic diseases combine Phases I and II to evaluate safety and preliminary efficacy. For data management purposes, all of these studies should be considered as Phase I.

Dr. Aguilar-Cordova summarized the RAC consensus that the RAC should concentrate on the Phase I category for the capture of a broader level of information; on the Phase II or Phase III categories, the RAC should capture only the adverse events and published citations.

Dr. McIvor inquired if the RAC should obtain protocol results on the basis of investigators' or sponsors' voluntary submission of those data prior to publication in professional journals. Dr. Aguilar-Cordova said that serious adverse effects should be reported. Dr. Glorioso noted that there are many forms of disclosure of data other than publication in journals, i.e., news release, conference abstracts, etc.

Dr. Ross stated that the number of accrued patients should be disclosed for all phases of studies. Dr. Mickelson said that progression of any study from Phase I to later stages should be reported.

Dr. Noguchi commented on the database. From his understanding, the investigators and sponsors are reluctant to disclose the data prematurely. When they are ready to disclose such data, they are willing to comply with such a requirement. Dr. Noguchi suggested keeping all the data fields proposed for data management open. For Phase I studies, there is little disagreement regarding disclosure. The FDA's annual reports are due on the protocol anniversary dates, and the RAC annual reports are due on another set date.

Mr. Kradjian noted that sponsor's concern is premature disclosure including data on the number of patients.

Ms. Binko was concerned about the Phase III studies. The publicly disclosed enrollment data might be used in many ways not intended by data management, e.g., by Wall Street analysts to make their recommendation regarding stock trading. In double-blinded Phases II and III trials that include a control group receiving a placebo in the study, it is impossible for a sponsor to report adverse effects related to any gene therapy procedure before unblinding. Ms. Binko said that most companies would feel comfortable in reporting serious adverse effects related to gene transfer technology. Once the study is completed, the companies would have no problem disclosing the number of accrued patients in their studies.

Dr. Lysaught inquired how FDA deals with adverse events reports regarding the double-blinded studies. Dr. Noguchi stated that FDA's medical officers together with its product reviewers determine whether the seriousness of the adverse events require unblinding the study. The most serious effects should be already discovered at the earlier stages of the study before advancing to Phase III.

Dr. Alex Kuta (Genzyme Corporation) noted that most adverse effects should be obvious before a protoco moved to the Phase III product development stage. The RAC should limit its data management to Phases I and II studies. The efficacy question of Phase III studies will not be answered until the full analysis of the data after completion of the studies.

Dr. Glorioso agreed that the goal of the RAC is to provide information to the public and that this function can be fulfilled by a report after the studies are completed. The real time analysis of adverse events is an FDA function. Dr. Ross agreed to Dr. Glorioso's statement. The FDA may inform the RAC if it has any compelling reason to disclose any serious adverse events. Dr. Noguchi agreed.

Dr. Aguilar-Cordova suggested that the RAC can provide an analysis of the safety of the trials conducted to date. These studies have involved more than 5,000 patients with vectors ranging from retrovirus to plasmid DNA. These data can be used to assure the public that gene therapy is safe. Dr.Glorioso was reluctant to have the RAC provide direct analysis of product development. The RAC should provide the public with information regarding new technology and its safety; he preferred FDA to deal with Phase III product development issues.

Dr. Wolff preferred to have some information in data management for any trials which have progressed to the Phase II/III stages. Dr. Ross agreed that information such as the names of investigators, the target disease, and some basic information of the trials should be included.

Dr. Donald Gay (Chiron Corporation) was concerned about disclosure of proprietary information regarding Phases II and III trials for fear of adverse impact on the company's finances and internal goals and objectives. All the adverse events are reported to FDA; it is not appropriate for the RAC to require reporting of the later stage trials.

Dr. Noguchi stated that Phase II and Phase III disclosures are made only after discussion with thesponsor. Any given company should not be penalized for making extra effort to uncover an adverse effect; the disclosure should be handled with sensitivity to focus on the generic issue and not on a specific product or a company. Dr. Aguilar-Cordova inquired if FDA will inform the RAC regarding an unexpected adverse effect, e.g., germ line alteration detected in a large scale Phase III trial. Dr. Noguchi responded that he is unable to answer such a hypothetical question. He preferred to have a generic discussion rather than to discuss a specific case. Dr. McIvor preferred such a disclosure be made on a voluntary basis from the investigators or sponsors.

Dr. Aguilar-Cordova asked if the RAC would entertain a motion regarding the Phase III protocols. Dr.Kuta said that in the gene transfer field especially dealing with a rare disease, it is often difficult to delineate the boundaries of Phases I, II, and III trials; it is prudent not to single out a cut-off phase for data management. Ms. Knorr suggested that Data Management Subcommittee continue to deliberate this issue and report back to the RAC. Dr. McIvor agreed.

Drs. McIvor and Markert preferred to make reporting on Phase III trials voluntary; Drs. Wolff and Aguilar-Cordova noted that some basic information should be required of the investigators or sponsors.

Dr. Markert was concerned about confidential information in the electronic database; the security could be breeched by computer hacking. Dr. Noguchi said that FDA has taken into account the computer security issue.

Dr. Aguilar-Cordova concluded the discussion by stating that the issue of capturing the information of Phase III protocols will be discussed by the Data Management Subcommittee and the subcommittee will report back to the full RAC.

XII. HUMAN GENE THERAPY PROTOCOLS NOT REQUIRING FULL RAC REVIEW

Ms. Knorr noted that 9 gene transfer protocols have been exempted from full RAC review since December 9, 1996, RAC meeting. The categories of these protocols are as follows: (1) 5 cancer immunotherapy, (2) 1 cancer pro-drug protocol, (3) 2 cancerchemoprotection, and (4) 1 monogenic disease for CF. Summaries of these protocols were reviewed by RAC members, and the following 9 protocols are recommended by RAC members to be exempt from full RAC discussion.

These 9 protocols are as follows:

9611-165

Rosenberg, Steven A., NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended by NIH/ORDA: 1-17-96.

9611-166

Rosenberg, Steven A., NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Vaccinia Virus Encoding the MART-1Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended by NIH/ORDA: 1-17-96.

9611-167

Maria, Bernard, et al. (All #9608-157 sites are eligible to participate in this study.)*A Prospective, Open-Label, Multicenter, Extension Trial for the Treatment of RecurrentGlioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115.*

This protocol is an extension of #9608-157.

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97.

9611-168

Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; Klasa, Richard, British Columbia Cancer Agency, Vancouver, B.C., Canada; Gonzales, Rene, University of Colorado Cancer Center, Denver, Colorado; *Phase II Study of Immunotherapy ofMetastatic Melanoma by Direct Gene Transfer.*

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97.

9611-169

Hersh, Evan, M., Arizona Cancer Center, Tucson, Arizona; Rinehart, John, Scott and White Clinic, Temple, Texas; Rubin, Joseph, Mayo Clinic, Rochester, Minnesota; Sondak, Vernon K., University of Michigan Medical Center, Ann Arbor, Michigan; *Phase I Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.*

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-17-97.

9612-170

Sorscher, Eric, University of Alabama, Birmingham, Medical Center; *Safety and Efficiency of Gene*

Transfer of Aerosol Administration of a Single Dose of a Cationic Lipid/DNA Formulation to the Lungs and Nose of Patients with Cystic Fibrosis.

NIH/ORDA Receipt Date: 12-17-96**.** Sole FDA Review Recommended by NIH/ORDA: 1-6-97.

9701-172

Cornetta, Kenneth, and Abonour, Rafat, Indiana University Department of Medicine, Indianapolis, Indiana; *High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study.*

NIH/ORDA Receipt Date: 1-9-97. Sole FDA Review Recommended by NIH/ORDA: 2-26-97.

9701-173

Williams, David A., Indiana University School of Medicine, Indianapolis, Indiana; *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^6-Methylguanine DNA Methyltransferase.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-4-97.

9701-174

Das Gupta, Tapas K., University of Illinois at Chicago, Chicago, Illinois; *A Pilot Study Using Interleukin-2 Transfected Irradiated Allogeneic Melanoma Cells Encapsulated in an Immunoisolation Device In Patients with Metastatic Malignant Melanoma.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-21-97.

Other Comments

Dr. Wolff noted that three RAC members recommended full RAC discussion of Protocols #9611-165 and #9611-166 by Dr. Rosenberg. Ms. Knorr explained that these two protocols were submitted in the interim period of adopting the new rule of requiring a minimum recommendation of three RAC members to trigger a full RAC review; the current *NIH Guidelines* permits ORDA to make the exempt decision.

Dr. Lysaught noted that in Protocol #9701-173, she asked the investigator to address her concern about involving children in this study; she noted that an exempt letter was sent to the investigator before her concern was addressed. Dr. Aguilar-Cordova and Ms. Knorr noted that ORDA needs to inform the investigators within 15 working days regarding the exempt decision or the need for full RAC review. Dr. McIvor noted that only two RAC members recommended full RAC discussion, while six members recommended exemption. Dr. Lysaught was concerned that a minority opinion was not considered in the exempt decision. Dr. Noguchi noted that the FDA similarly needs to make a decision within 30 days even though not all reviewers are unanimous in their opinion. Dr. Aguilar-Cordova noted that Dr. Lysaught's concern about children was stated in the letter to the investigator; a protocol cannot be held back if a single RAC member has a question not responded to by the investigator. Dr. Saha agreed that it is up to the investigator to respond to the query. Ms. Knorr suggested that a solution to this problem is to have the

RAC members fax to ORDA their concerns as early as possible; such concerns will be circulated to other RAC members in order to have an exempt decision made within 15 working days. Dr. Aguilar-Cordova noted that if there is a complex issue not resolved in time, the 15 day period can be extended.

Dr. Markert stated that the NIH has guidelines to ensure that women and minority are included in clinical trials. As a pediatrician, she received last week a proposed guideline mandating inclusion of children in clinical protocols. For all clinical trials, there may in the future need to be justification for not including children.

Dr. McIvor noted that a recombinantfowlpox virus used in Protocol #9611-165 appears to be a new vector. Dr. Smith noted that Protocol #9610-163 (Rosenberg) was the first protocol using recombinant fowlpox virus. During the December RAC meeting, there was a discussion regarding the Rosenberg protocol because it was exempted from RAC review by ORDA duringthe period that the RAC's role in protocol review was not defined. Dr. Noguchi noted a history of including fowlpox and vaccinia protocols in human gene transfer studies. The first protocol of recombinantvaccinia virus expressing the carcinoembyonic antigen (CEA) by Dr. Jeff Schlom of NIH, was exempted from RAC review by applying the criteria of Appendix M-IX-A, *Footnote to Appendix M*. This footnote excludes vaccine studies from RAC purview. Subsequently, this footnote was amended at the March 1994 RAC meeting to limit vaccine exclusion to vector-encoding microbial immunogen. Under the new definition of vaccine, vaccinia-CEA protocol is considered as a gene transfer protocol under the purview of the RAC. Dr. Aguilar-Cordova noted that the RAC might want to revisit the vaccine exclusion; potentially some vaccine studies employing herpesvirus or lentivirus will not come under RAC purview. Dr. Noguchi said that at the present time, a lot of vaccine studies are outside the RAC purview.

Regarding Dr. McIvor's question of the fowlpox virus protocols, Ms. Knorr noted that in the future, t situation will be corrected as the new RAC process is in effect. Dr. Ross noted that the RAC has discussed the issue of poxvirus vectors; fowlpox appears to be a safe viru

XIII. CONTINUED DISCUSSION OF PROTOCOL #9701-171--PUBLIC COMMENTS

Dr. Andrew Braun (Massachusetts General Hospital) expressed his concerns as a member of the public regarding the RAC approval of Dr. Crystal's protocol of using normal subjects in his study of recombinant adenovirus (Protocol #9701-171). He was concerned about some permanent changes induced by the adenovirus vector to a normal individual. Germ line transmission is only one concern, and he noted that immune response induced by the vector is a long lasting change. He said that the possibility of long-term chronic expression by the vector unanticipated by the investigator is real; he cited examples of unexpectedly long-term expression of transgenes found in Dr. Cry's CF protocol and the protocol of severe combined immunodeficiency due to adenosine deaminase deficiency (SCID -A

Dr. Braun said that a precedent has been set by the RAC for allowing a human gene transfer experiment to be performed on normal subjects despite the disclaimer that RA's approval of Dr. Cryst's protocol should not be construed as a precedent. Dr. Braun was disturbed by the assertion by the investigator that the normal subjects are more capable of giving "true" informed consent to a gene transfer study. If a physician believes that a desperately ill patient is not capable of giving a "true" informed consent; it is an intellectual dishonesty to accept the Informed Consent document to perform a gene transfer experiment on such a seriously ill patient. Dr. Braun was concerned by the use of the term "treatment" in the Informed Consent document; such a terminology has special connotations to the subjects to infer some expected benefit. He did not believe that normal individuals are more likely to give "true" informed consent; the normal volunteers are enticed by monetary inducement. Dr. Braun emphasized that the permanent consequence of gene transfer to a normal subject is similar to a surgical scar resulting from participating

in a surgical experiment. Dr. Braun admired the courage of Ms. Abbey Meyers, a former RAC member, to raise similar issues to those he mentioned.

Dr. Noguchi remarked that in almost all areas of drug development other than gene therapy, the first use in humans is in normal volunteers usually motivated by altruism of the volunteers to help advancing medical knowledge. Dr. Noguchi noted that permanent changes and informedconsent document issue raised by Dr. Braun are not unique to gene transfer studies except the issue of germ line alteration; he noted the endotoxin testing on normal volunteers of some product developments raises similar concern as the present study.

Dr. McIvor noted that most of the issues raised by Dr. Braun were deliberated before RAC approval of Dr. Crystal's protocol. Dr. Aguilar-Cordova agreed. Dr. Saha noted that immunity induced by the vector an its transgene is not as permanent as Dr. Braun alluded to; some immune response disappears afte immunogen administratio

XIV. DATA MANAGEMENT -- SAFETY REPORTS, AMENDMENTS AND UPDATES/SMITH

Dr. Smith noted that a total of 174 human gene transfer protocols have been registered with ORDA . Th is a new category of non-therapeutic protocols exemplied by Dr. Crystal's protocol (#9701-171) that does not belong to either gene therapy nor gene marking category.

Dr. Smith noted that the majority of adverse event reports are minor complications of underlying diseases except reports relating to adenovirus vector induced inflammation in CF trials. The other most noticeable events have occurred in Protocol #9303-037 (Van Gilder, et. al., brain tumor protocol) using the Herpes simplex virus thymidine kinase (HSV-TK)/ Ganciclovir strategy. Mild to severe meningeal i occurred in 15 of the 30 treated patients after administration of the VPC to the brain. In 8 out of 30 pati vector sequences were detected by the PCR technique in the blood samples presumably due to leaka of VPC to the vasculature in the brain. Dr. Smith noted that 3 patients experienced brain edem

Dr. Smith said that flu-like symptoms were noted in one Hunter Syndrome patient treated in Protocol #9409-087 (Whitley) by infusion of gene-modified lymphocytes. Dr. Wolff asked if similar flu-like symptoms were noted in other adoptive cell infusion therapies. Dr. Noguchi responded affirmatively.

XV. DISCUSSION REGARDING COMPLIANCE UNDER THE *NIH GUIDELINES* / KNOR

Ms. Knorr stated that since the December 9, 1996, RAC meeting, ORDA has informed the Chairs contact persons of IBCs , and investigators of human gene transfer protocols about the procedures fo submission of human gene transfer protocols. Appendix M-1.*Submission Requirements -- Human Gene Transfer Proposals* of the *NIH Guidelin*has not been revised.

XVI. NIH /FDA STRATEGIES TO STREAMLINE REVIEW AND APPROVA PROCEDURES/ KNORR AND MILLER

Ms. Knorr asked Dr. Miller to present her letter to the RAC dated February 23, 1997, regarding an upda on mechanisms for interactions between ORDA and Center for Biologics Evaluation and Researc (CBER) of FDA. Dr. Miller stated that CBER representatives have been working internally within FD with ORDA staff to define mechanisms for interaction between these two organizations. Dr. Mille summarized in her letter 4 areas of activities that are underway atCBER to improve communications w ORDA and coordinate efforts toward the resolution of common issues, i.e., confidential information identification of topics for early discussion, unified submission format, and CBER regulation to provid

public access to gene transfer IND informatio

Dr. Miller stated that CBER representatives are working with FDA General Counsel to negotiate the ter for release of limited information regarding Gene Therapy IND submissions received by CBER (suc sponsor, title, indication) to ORDA staff for use in oversight of NIH funded studies. While generally employees are bound by regulations on confidentiality of information, as stated in 21 CFR 601.50 (a) "The existence of an IND notice for a biological product will not be disclosed by the FDA unless it ha previously been publicly disclosed or acknowledged." It may be possible to disclose FDA records to other Federal government departments and agencies, such as NIH / ORDA ; however, this disclosure woul subject ORDA personnel to the same restrictions with respect to the disclosure of such records as an FDA employee. Therefore, the information provided may not be publicly disclosed; ORDA may use thi information to exercise oversight functions regarding requirements for submission of information as laid out in the *NIH Guidelin*

Dr. Miller envisioned the process as follows. Upon receipt of an IND , FDA would forward the informatio to ORDA and then attach a copy of FDA acknowledgment letter to the IND sponsor. In acknowledgment letter, FDA would alert the sponsor to his or her responsibility to comply with the *NIH Guidelines*. ORDA would then be able to contact the investigators if they are not in compliance with th submission requirements of *NIH Guidelin* Within the 30 day requirement of IND decision, the RAC m decide on if the protocol would require full RAC review. Ms. Knorr noted that ORDA may use its IF IBC contacts to help ensure all investigators are in compliance with the *NIH Guidelin*

Dr. Miller stated that the second area of the FDA plan is to identify topics for early discussion: protocols that raise novelty and ethics issues that would benefit from RAC discussion. Ms. Knorr noted that thi early information will be useful for NIH to plan for the GT

Other Comments

Dr. Aguilar-Cordova noted that one scenario of the FDA plan is that a protocol could potentially be discussed at the RAC meeting after FDA approval at the end of 30 day statutory deadline. Dr. Miller responded that FDA is considering advising the investigator to delay initiation of a protocol pending RAC review.

Dr. Noguchi stated that FDA has legal authority to put an IND on clinical hold if there is not sufficien information to assess the safety issue of risk and benefit until an advisory committee is convened to discuss the issue. Dr. Aguilar-Cordova inquired whether it would be a sufficient justification to put a protocol on clinical hold if 3 RAC members recommend full RAC review of such a protocol. Dr. Noguchi responded that a decision will be made on a case-by-case basis if FDA finds such a necessity.

Ms. Knorr noted that the timing issue arises partly from the investigatfailure to comply withthe *NIH Guidelines* for simultaneous submission of the protocol to NIH and FDA as illustrated in Dr. Crystcase in which Dr. Crystal obtained FDA approval before RAC review. A clinical hold on a protocol pending RAC review would allow the RAC to have a chance to discuss the novel protocol. Dr. Ross agreed that an after-the-fact discussion by the RAC of a protocol that has already been approved by FDA is not going to reflect well on FDA. Dr. Noguchi responded that legally FDA is the agency charged with assuring the safety and effectiveness of gene therapy products while the RAC is not. FDA looks to public discussion to establish scientific issues in order for FDA to make safety evaluation. Dr. Noguchi did not consider it a meaningful exercise for the RAC to duplicate FDA function. However, there are occasions that FDA would consider clinical hold of a protocol. Dr. Noguchi cited a recent example of an xenotransplant protocol involving transplantation of baboon bone marrow to a patient with acquired immunodeficiency

syndrome (AIDS). In this particular case, the advisory committee meeting was convened after the 30 day statutory deadline, and FDA decided to put that protocol on clinical hold pending public discussion by the advisory committee.

Dr. Wolff inquired whether the RAC or FDA's own advisory committee would be asked to conduct public discussion of a gene transfer protocol. Dr. Noguchi responded that in the case of gene transfer protocols, FDA would defer to the RAC for deliberation. Drs. Wolff and Aguilar-Cordova inquired if the FDA would request RAC review on the basis of safety or ethics issue alone. Dr. Noguchi clarified that the FDA is unable to stop a protocol on the basis of scientific validity if the protocol is considered as safe in relation to the patient population being studied. Similarly, the FDA does not have sufficient legal base to stop a protocol simply on ethical or societal concerns if the safety issue has been adequate addressed; as an example of germ line gene therapy, the FDA would have no guidance if the ethical issue has not been addressed by a public body.

Dr. Aguilar-Cordova asked how the FDA would deal with an enhancement gene therapy protocol if it were submitted before the proposed GTPC discussion of the issue. One example offered by Dr. McIvor is a adenovirus protocol to treat baldness. Dr. Noguchi stated that in this particular example FDA will be able to hold the protocol on the basis of a safety concern; an FDA researcher has recently found that abnormal insertion of a normal gene into the chromosomes of an organism has deleterious effects on the organism.

Dr. Saha inquired if in the future FDA would stop a protocol such as Dr. Crystal's which deals with a novel issue of involving normal individuals. Dr. Noguchi did not directly responded to this question. If the FDA's plan on its future interaction with ORDA is enacted, the FDA would alert ORDA that such a protocol has been submitted to the FDA. Dr. Saha asked that if the RAC decides to review such a protocol at the forthcoming RAC meeting, would the FDA put a clinical hold on such a protocol? Drs. Miller and Noguchi responded that FDA does not have a formal mechanism to place a clinical hold on a protocol pending full RAC review. Dr. Lysaught noted that in the case of a *in utero* gene therapy protocol, Dr. Noguchi responded to the RAC at the December 1996 meeting that the FDA would put an *in utero* gene therapy protocol on clinical hold pending RAC discussion. Dr. Noguchi stated that in the real world it is unlikely that there would be no safety concern for the cutting edge protocols. Ms. Knorr noted that if the protocol receives any NIH funding, it would have to be in compliance with the *NIH Guidelines*, i.e., the protocol cannot be initiated prior to either: (1) receiving an exemption letter from NIH, or (2) subsequent to full RAC discussion. Dr. Ross preferred that the FDA would coordinate with NIH to advise the investigators not to initiate the protocol until after RAC discussion. Dr. Noguchi responded that the FDA is working in the direction that Dr. Ross suggested.

Dr. Aguilar-Cordova noted that if an investigator has already recruited patients onto his or her protocol before RAC *discussion*, it would put the RAC in a very awkward situation. Dr. Wolff was concerned that the RAC would not be able to hold a protocol until after its discussion. Ms. Knorr noted that the RAC's strength is its public persuasion; its recommendation will go to the NIH Director and will be noted by other agencies including IBC, IRB, OPRR, and

Dr. Aguilar-Cordova called on the RAC to address the issue of whether it is still useful to discuss a protocol after patients have been recruited, or if there should be a mechanism to ensure that a novel protocol will not be initiated prior to RAC discussion. Dr. Lysaught said that it is still important for the RAC to hold public discussion even if the protocol had already been initiated; for a safe novel vector such as the fowlpox virus, the public discussion is useful to allay public fears of the new technology. Dr. Saha agreed that the RAC as a public body should discuss the novel technology without the time frame of whether it has already been initiated or not. Dr. Markert also agreed that if it is something novel, the RAC should discuss it in the open forum including the complete submission materials.

Dr. Mickelson said that she prefers RAC discussion of a protocol before its initiation. Dr. Ross noted that for a really "novel" protocol, the RAC discussion should precede the initiation of the protocol. Dr. Markert clarified her position that she agrees with Dr. Ross' statement. Dr. Glorioso was concerned that th investigators will have no incentive to go through the RAC process if they may initiate a study before RAC discussion. Dr. McIvor noted that a prudent investigator would wait until a RAC discussion if he or she is proposing to use a lentivirus vector for gene therapy studie

Dr. Aguilar-Cordova suggested the RAC propose a motion regarding a mechanism to hold a protocol until RAC discussion.

Dr. Markert did not favor an universal mechanism that will stop initiation of all protocols recommended full RAC discussion prior to RAC review of the protocols. She cited the fowlpox as an example; it ha been used in many vaccine studies, and she would not be in favor of holding up such a proposal. Rather the RAC could discuss the use of the fowlpox virus in gene therapy trials. Dr. Markert , however, fav that in some cases, the RAC should be able to hold up a protocol.

Ms. Binko (Cell Genesys) suggested a solution to the conundrum posed by the timing issue of review. She suggested that the RAC waive the requirements for having IRB and IBC approvals prior t entertaining a protocol. FDA regulation allows simultaneous submission to FDA, IRB , and IBC. She sai that if the RAC considers a protocol in the pre- IND stage, it could easily be able to discuss a protoco before any patients are entered into a study.

Dr. Saha inquired if FDA requires IRB and IBC approvals. Dr. Noguchi responded that all clini protocols may not be initiated without IRB approval. FDA does not require the approvalin a sequent process; he does not favor that the RAC use IRB and IBC approvals as a prescreening process. Dr. S remarked that he would doubt any IRB or IBC would reject a protocol after its approval by FD

Dr. French Anderson (University of Southern California) made a historical observation. At the early years of gene therapy clinical trials, the reason that the RAC adopted the rule of requiring prior IRB and IB approvals was to prevent inappropriate protocols from being submitted by the investigators to the RAC without notifying their institutions; there were sufficient publicity and media spotlights over the gene therapy proposals at that time. Dr. Anderson agreed with Dr. Noguchi that there is no reason to maintain the historically important but presently irrelevant requirement of prior IRB and IBC approvals before RA review. Dr. Anderson noted that his IRB expects FDA approval before they make a decision regarding clinical protocol. For gene transfer protocols, most IRBs give tentative approval to allow submission t NIH / ORDA in compliance with the submission requirement of *NIH Guidelin*

Ms. Knorr noted that IRB is not within the purview of the RAC while IBC is. She said that the structu the *NIH Guidelin*is based on the concept of the investigators seeking their local institutional approvals first before their protocols are reviewed by the RAC. Removal of the IBC approval requirement would fundamentally change the structure of the *NIH Guidelin*

Dr. Wolff made an observation from his experience of serving on an IBC. He said that most IBCs do no have adequate expertise in dealing with the safety issues of novel gene transfer protocols. He prefers that a novel protocol first be reviewed by the RAC and then receive final approval from IBC; most of the gene transfer protocols that are not deemed to be novel by the RAC should be handled by IBC by itself.

Dr. Markert favored the notion that the investigators be allowed to submit their protocols in parallel to a agencies, and the IBC be notified by ORDA regarding the RAC decision on the exempt/review status p

to giving the final approval of protocols.

Dr. Ross was concerned that the RAC would not have the final version of the protocols after amendments have been made by the investigators responding to various reviews. Ms. Knorr noted that the *NIH Guidelines* may require the investigators to notify ORDA regarding any changes made to their protocol. Dr. Noguchi noted that most changes of the protocols are likely to be in response to FDA recommendations, and FDA will address the issue of informing the RAC regarding its recommendations to protocol modification. Dr. Aguilar-Cordova noted that local institutions have final authority of granting approval to the protocols to be conducted at their institutions.

Dr. Wolff proposed a motion to require the gene transfer protocols be simultaneously submitted to both the IBC and the RAC, and the final IBC approval should not be granted until the IBC is notified by ORDA regarding the RAC decision on the exempt/review status of the protocol.

Dr. McIvor proposed a motion to remove the requirement of prior IBC and IRB approvals from th submission requirement of the RAC. Dr. Wolff stated that Dr. McIvor's motion should be considered as a separate motion from his proposal.

Dr. Wolff said that the investigators need to notify the institution that a protocol is being submitted to the RAC. Dr. Markert noted that these two motions address two separate issues and should be vote separately. Dr. Aguilar-Cordova suggested that the RAC consider Dr. McIvor's motion first and then vote on Dr. Wolff's motion.

Dr. McIvor made a motion to remove the requirement for IBC and IRB approvals prior to RAC submiss Dr. Markert seconded the motio

Dr. Saha inquired if Dr. McIvor's motion would be consistent with FDA regulation. Dr. Noguchi responded affirmatively. Dr. Lysaught was concerned that the RAC would be reviewing protocols in the developme stage of the protocol. Dr. Ross responded that Dr. Lysaught's concern stemmed from the past experience that the RAC would be functioning as consultants to help investigators develop their protocols. Dr. Ross noted that since the RAC is now only reviewing novel protocols, such a tutorial role is appropriate. Dr. Wolff noted that such a change of submission requirement would avoid the scenario where the RAC has to review a protocol after its FDA approval. Ms. Knorr noted that the RAC would have more influence o the protocol development in the new arrangement. Mr. Kradjian stated that to remove prior IRB and approvals from RAC submission is a significant step toward streamlining the overall review procedure.

Committee Motion 11

A motion was made by Dr. McIvor and seconded by Dr. Markert to remove the requirements for prio approvals of the IRB and IBC from the Appendix M-*Submission Requirements -- Human Gene Transfer Proposals* of the *NIH Guidelin* The motion passed by a vote of 8 in favor, 0 opposed, and no abstentions.

Dr. Wolff restated his motion to require investigators to simultaneously submit their protocols to IBC and the RAC, and final IBC approval of the protocols should be pending on RAC decision to exempt the protocols or subsequent to full RAC discussion, if applicable.

Dr. Mickelson and Ms. Knorr suggested simultaneous IBC notification instead of submission of the who protocol to IBC. Dr. Wolff was concerned that without the whole protocol submission IBC might not be able to have input to the RAC regarding local concerns of the protocols.

Dr. Lysaught asked why IRB, which deals with human subjects issues, is not included in the proces Knorr and Dr. Wolff responded that IBC but not IRB is directly under the purview of *NIH Guidelin* Dr. McIvor noted that RAC discussion of the novel protocols would benefit both IBC and IRB in thei review; he would not favor requirement of simultaneous submission to IBC. Dr. Wolff said that the local IRB and IBC should have final authority to approve clinical protocols; the RAC will address mostly th novelty issues. Dr. Noguchi pointed out a potential problem that might result from simultaneous submission to and review by different agencies. He noted that different agencies have their different charges, i.e., the RAC for public discussion of ethical and societal issues, IBC for recombinant DNA safety issues, IRB for issues of patient rights, and FDA for safety of the overall protocol. Dr. McIvor stated that he favors retaining the current requirement of simultaneous submission to FDA and the RAC but to provide notification to IBC instead of full submission. Dr. Wolff accepted the friendlyamendment his motion to notify the IBC instead of simultaneous submission to IBC. Dr. Aguilar-Cordova stated that IBC will give final approval after receiving feedback from the RAC. Dr. Lysaught said that IBC should n give final approval prior to RAC decision on exempt/review status. Ms. Knorr said that such a prio requirement of RAC decision could be codified in the *NIH Guidelin* Dr. Lysaught seconded Dr. Wolf motion.

Mr. Kradjian noted that for protocols sponsored by a company there may be a problem of simultaneou notification of IBC; a sponsor may submit a protocol to the RAC prior to identifying an institution to conduc the clinical trial. Dr. Allgood added that in some instances an investigator may be yet to be identified. D Aguilar-Cordova responded that NIH would have no jurisdiction if there is no NIH -funded investigato institution.

Drs. Miller and Noguchi were concerned about simultaneous submission of Appendix M materials to the RAC and FDA. Dr. Aguilar-Cordova said that the issue is separate from the IBC/RAC submission issue.

Committee Motion 12

A motion was made by Dr. Wolff and seconded by Dr. Lysaught to streamline the RAC/IBC revie procedure. A human gene transfer protocol should be submitted to NIH / ORDA with simultane notification to IBC. Final IBC and IRB approvals should be submitted to ORDA upon receipt of following: (1) NIH notification of exemption from full RAC discussion, or (2) subsequent to full RA discussion (if applicable). Human gene transfer clinical trials shall not be initiated prior to submission of final IBC and IRB approvals to the NIH . The motion passed by a vote of 8 in favor, 0 opposed, and abstentions.

Dr. Aguilar-Cordova asked the RAC to comment on the issue of simultaneous submission to the RAC and FDA. Dr. Miller noted that the issue can be discussed within the context of an unified submission format. Dr. Markert suggested that there is no need of simultaneous submission; Appendix M can come to th RAC at the pre- IND stage of the negotiation with FDA, i.e., before formal IND submission to FDA. Mickelson inquired if there is any formal FDA regulation that governs the pre- IND phase. Dr. Noguch responded that at the present time, pre- IND meeting is an informal process but it is well understoo among the gene therapy community. Dr. Mickelson said that the RAC should focus its attention at the pre- IND phase of a protocol development where it has the biggest impac

XVII. CLOSING REMARKS/AGUILAR-CORDOVA

Dr. Aguilar-Cordova stated that it has been a productive meeting that has come up with some specific recommendations. He asked the RAC to suggest any issues to be addressed at the next RAC meeting.

Dr. Mickelson stated that the RAC should further discuss the mechanism that would allow the RAC to entertain gene transfer protocols at the early stage of protocol development. Dr. Markert said tha investigators should be allowed to submit to the RAC before their interaction with FDA.

Dr. Anderson stated that the RAC has come to a full circle with respect to protocol review. In the early days, the RAC had helped shepherd the investigators to improve their protocols; as the number of protocols increased, the RAC demanded fully polished protocols for review; and now that the RAC has opted to review only the novel protocols, the RAC should be involved in the earliest stages and should help the investigators to make sure that the final protocols are appropriate. Dr. Mickelson noted that the RAC is the most influential at the early stage of protocol development. Dr. Anderson said that rather than duplicating FDA function, it is important to retain the RAC to help delineate the ethical and societal issues of gene therapy research.

XVIII. FUTURE MEETING DATES/AGUILAR-CORDOVA

The next meeting of the RAC will be June 12-13, 1997, at the National Institutes of Health, Building 31C, Conference Room 6.

XIX. ADJOURNMENT/AGUILAR-CORDOVA

Dr. Aguilar-Cordova adjourned the meeting at 3:30 p.m. on March 7, 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: July 7, 1997

C. Estuardo Aguilar-Cordova, Ph.
Acting Chair
Recombinant DNA Advisory Committee
National Institutes of Health