DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
March 8-10, 2000

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

March 8-10, 2000

The Recombinant DNA Advisory Committee (RAC) was convened for its 77th meeting at 9:00 a.m. on March 8, 2000, at the National Institutes of Health (NIH), Building 31, Sixth Floor, Conference Room 10, 9000 Rockville Pike Bethesda, MD 20892. Dr. Claudia A. Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on March 8 from 9:00 a.m. until 4:30 p.m., on March 9 from 8:00 a.m. until 6:40 p.m and on March 10 from 8:00 a.m. until 3:10 p.m. A committee roster is attached (Attachment I). The following individuals were present for all or part of the meeting:

Committee Members:

C. Estuardo Aguilar-Cordova, Baylor College of Medicine

Dale G. Ando, Cell Genesys, Inc.

Xandra O. Breakefield, Massachusetts General Hospital

Louise T. Chow, University of Alabama, Birmingham

Theodore Friedmann, University of California, San Diego

Jon W. Gordon, Mount Sinai School of Medicine

Jay J. Greenblatt, National Cancer Institute, National Institutes of Health

Eric T. Juengst, Case Western Reserve University

Nancy M.P. King, University of North Carolina, Chapel Hill

Sue L. Levi-Pearl, Tourette's Syndrome Association, Inc.

Ruth Macklin, Albert Einstein College of Medicine

M. Louise Markert, Duke University Medical Center

R. Scott McIvor, University of Minnesota

Claudia A. Mickelson, Massachusetts Institute of Technology

Jon A. Wolff, University of Wisconsin Medical School

Executive Secretary:

Amy P. Patterson, National Institutes of Health

Ad Hoc Consultants, Speakers, and Principal Investigators:

V. Elayne Arterbery, Barbara Ann Karmanos Cancer Institute

Gustavo Ayala, Baylor College of Medicine

Martha C. Bohn, Northwestern University Medical School

Jeffrey S. Chamberlain, University of Michigan

Matthew During, Thomas Jefferson University

Gary B. Ellis, Office of Protection from Research Risks,NIH

Bertil Glader, Stanford University

Frank Graham, McMaster University (Canada)

John T. Hamm, University of Louisville

Michael J. Iadarola, National Institute of Dental and Craniofacial Research, National Institutes of Health

Mark A. Kay, Stanford University

Kamel Khalili, Temple University

Mark W. Kieran, Dana-Farber Cancer Institute

Donald B. Kohn, Children's Hospital, Los Angeles

Kenneth Krantz, Calydon

Paola Leone, Thomas Jefferson University

Brian J. Miles, Baylor College of Medicine

Nicholas Muzyczka, University of Florida

Stewart Newman, New York Medical College and Council for Responsible Genetics

Christine Pannunzio, Osiris Therapeutics, Inc.

Jeremy Rifkin, Foundation on Economic Trends

Frederick A. Simeone, Thomas Jefferson University

Max W. Sung, Mount Sinai School of Medicine

Gilbert C. White II, Hemophilia Treatment Center, University of North Carolina School of Medicine

George Wilding, University of Wisconsin Medical School

Savio L.C. Woo, Mount Sinai School of Medicine and American Society for Gene Therapy

Wei-Wei Zhang, GenStar Therapeutics Corporation/UroGen Corporation

Nonvoting/Liaison Representatives:

Daniel W. Drell, U.S. Department of Energy

Gary B. Ellis, Office for Protection from Research Risks, National Institutes of Health

Gilbert Fayl, Delegation of the Commission of the European Communities

Robert Frederick, U.S. Environmental Protection Agency

Philip Harriman, National Science Foundation

Daniel D. Jones, U.S. Department of Agriculture

Daniel P. Jones, National Endowment for the Humanities

Barbara Levin, National Institute of Standards and Technology

Melody H. Lin, Office for Protection from Research Risks, National Institutes of Health

Elizabeth Milewski, U.S. Environmental Protection Agency

Andra Miller, U.S. Food and Drug Administration

Philip Noguchi, U.S. Food and Drug Administration

National Institutes of Health Staff Members:

Krysztofs S. Bankiewicz, NINDS

Bobbi Bennett, OD

John T. Burklow, OCPL

Connie Caldwell, OD

Fabio Candotti, NHGRI

Sara Carr, OD

Christine Castle, OD

John Chiorini, NIDCR

Cheryl Corsaro, CSR

Anthony Craig, NHGRI

Melissa Enriquez, NHGRI

Gregory Frykman, NCI

Mary Groesch, OD

Naoki Hamajima, NHGRI

Richard A. Hess, NHGRI

Christine Ireland, OD

Jaya Jagadeesh, NHGRI

Bob Jambou, OD

Carolyn M. Laurencot, NCI

Becky Lawson, OD

Rebecca Link, NHLBI

Jay Lozier, NHGRI

Catherine McKeon, NIDDK

Marcia Meldrun, NIDCR

Mike Miller, OD

Richard Morgan, NHGRI

Makoto Otsu, NHGRI

Fran Pollner, OD/OIR

Gene Rosenthal, OD

Nava Sarver, NIAID

Shepard H. Schurman, NHGRI

Thomas Shih, OD

Sonia I. Skarlatos, NHLBI

Lana Skirboll, OD

Vaya Vagadeesh, NHGRI

Brian Vastag, NCI

Taizo Wadi, NHGRI

Zhili Zheng, NHGRI

Others:

Approximately 194 individuals attended this three-day RAC meeting. A full list of attendees appears in Attachment I

I. Call to Order and Day One Opening Remarks/Dr. Mickelson

Dr. Mickelson, RAC Chair, called the meeting to order at 9:05 a.m. on March 8, 2000. The notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on February 18, 2000 (65 FR 8618). Issues to be discussed by the RAC at this symposium and meeting included a report on recent events and issues in gene transfer research; a gene transfer safety symposium on internally deleted, helper-dependent adenoviral vectors; discussion of seven human gene transfer protocols; a discussion of the RAC Working Group on Adverse Event Reporting; a discussion with the Advisory Committee to the Director, NIH, Working Group on NIH Oversight of Clinical Gene Transfer Research; a discussion of the RAC Working Group on Adenovirus Safety and Toxicity; and a proposal from a member of the public for a moratorium o some human somatic gene transfer protocols using viral vectors.

Dr. Mickelson noted that nine protocols were originally scheduled to be reviewed at this meeting; however, two protocols were withdrawn after the investigators received RAC comments. The investigators for those two protocols stated that RAC suggestions will result in additional preclinical studies.

Dr. Patterson reviewed the "Rules of Conduct and Conflict of Interest for Special Government Employees," which governs the conduct of RAC members. She noted that citizens serving on Federal advisory committees, such as the RAC, are appointed as special Federal Government employees, and therefore, members of the RAC are subject to th same rules of conduct that apply to all Federal Government employees. The most salient issues are the rules of conduct that apply to relationships or interactions with Congress, the disposition of confidential material, and rules regarding conflict of interest. All such rules were provided to RAC members in their premeeting materials.

II. Recent Events and Issues in Gene Transfer Research/Dr. Lana Skirboll, NIH Office of Science Policy

Dr. Skirboll stated that the protection of clinical study participants is primal; because research is risky, minimizing ri is the first rule of order, and as such, all clinical research is subject to a complex system of oversight. Gene transfer research (GTR) holds extraordinary promise but is still a young science; because it has been growing up in the public eye, with media attention and enthusiastic investigators, GTR may appear more mature than it is. Development of new treatments is a slow process but, at the same time, the public expects rapid advances and striking breakthroughs.

The NIH is committed to the role of the RAC and to the oversight of GTR because of the potential benefit to patients, investigators, and the community at large. The Office of the Director of NIH believes the RAC has been doing "a terrific job." Ensuring continuous public discussion of GTR is important work, which was never made more clear than at the December 1999 RAC meeting. Many questions have been raised about noncompliance with adverse event (AE reporting. When, on the death of Jesse Gelsinger, the Office of Biotechnology Activities (OBA) asked for patient and

safety data related to adenoviral vectors, information came flooding in from the research community because of the desire to explore, review, and self-analyze. A working group was convened, the RAC agenda was expanded, and research community discussion ensued. Precipitating events from Jesse Gelsinger's death uncovered areas of oversight that were receiving inadequate attention, and nonreporting of AEs will not occur again.

Questions from a variety of stakeholders have been raised about the appropriate roles of the NIH, the RAC, the Office for Protection from Research Risks (OPRR), institutional review boards (IRBs), and the Food and Drug Administration (FDA). Dr. Skirboll provided a sampling of the questions raised by Congress, the press, the scientific community, and patients (in no particular order):

- Should the NIH restore approval authority to the RAC?
- Did the 1997 relinquishing of approval have an effect on the reporting of AEs?
- Should the NIH receive individual AE reports? If so, in what timeframe?
- How can NIH requirements of AE reporting be harmonized with FDA requirements?
- What should the NIH do with the AE reports it receives?
- Are AE reports proprietary?
- What about patient confidentiality?
- Should there be Data Safety and Monitoring Boards (DSMBs) for all phases of gene transfer trials?
- What are the different roles of the NIH and the FDA?
- Are the two agencies collaborating sufficiently?
- What should be done about the increasing number of concerns regarding financial conflict of interest?
- What more must be done to ensure patient safety?
- Are patients receiving adequate informed consent?
- Are IRBs keeping pace with the science?
- Do IRBs have the appropriate resources to do their jobs effectively?
- Should the oversight of GTR be any different from the oversight of any other arena of clinical research?
- Are clinical investigators well trained?
- Are clinical trials well monitored?

Many of these questions need to be dealt with directly, but there are divergent opinions about the right answers to these questions. The NIH is seeking advice in answering these questions; no conclusions have been formed yet. Time is critical; investigators and patients need to know the rules. Patients should not be reluctant to participate in GTR

trials, and investigators and sponsors should not abandon this area of research.

Two new U.S. Department of Health and Human Services (DHHS) initiatives were announced on March 7, 2000:

1. The FDA will require sponsors to routinely submit monitoring plans as part of the investigational new drug (IND) application, and the FDA will ensure that these plans are being followed. The FDA will notify all sponsors of clinical trials to supply information on quality-control data regarding cell banks and viral banks.

2. A series of gene transfer safety symposia will take place, modeled on the success of the December 1999 RAC meeting discussion on adenovirus safety and toxicity. These symposia will enhance patient safety by bringing together investigators and the public to learn about safety issues and AE concerns, focusing on topics such as vectors, particular diseases, and specific populations.

Dr. Skirboll reminded the RAC that patients and their families are watching the RAC's actions and are hoping that new treatments are developed that will reduce suffering.

RAC Comments and Questions

Dr. Noguchi stated that the FDA seeks and encourages advice from the RAC and from the public on the timely but difficult issues surrounding GTR.

As RAC chair, Dr. Mickelson added a personal note that the RAC recognizes other stakeholders in the area of GTR—including industry and patient groups—and that those important others should understand that the RAC solicits and listens actively to their input.

III. Gene Transfer Safety Symposium: Internally Deleted, Helper-Dependent Adenoviral Vectors

Co-Chairs: Drs. Aguilar-Cordova and Ando

Sample Protocol: A Phase I, Single-Dose, Dose-Escalation Study of MiniAdFVIII Vector in Patients With Severe Hemophilia A (Protocol #0001-372)

Ad Hoc Consultants: Dr. Jeffrey S. Chamberlain, University of Michigan

Dr. Frank Graham, McMaster University, Canada (written review)

Dr. Mickelson stated that the FDA requested that this protocol be brought to the RAC. She also explained that the purpose of this symposium is to use this particular case and the experience of these investigators, who have worked out the details of this protocol, to engage in a dialog about generic issues related to this kind of virus.

Presentation on Internally Deleted, Helper-Dependent Adenoviral Vectors

Dr. Gilbert White II, Hemophilia Treatment Center, University of North Carolina School of Medicine, Chapel Hill

Dr. White introduced his colleagues and stated that the Hemophilia Treatment Center at the University of North Carolina, Chapel Hill, is the second largest hemophilia center in the United States. The Center has a long tradition of clinical research, and Dr. White provided a history of the Center's contribution to hemophilia research. As Chair of the

Research Working Group at the National Hemophilia Foundation (NHF), Dr. White strongly believes that gene transfer ultimately will provide an important treatment approach for patients with hemophilia. Patients served at the Center and their families also believe in the potential for GTR.

Dr. White provided background information on hemophilia A, a severe bleeding disorder. Patients with a Factor VIII (FVIII) level of less than 1 percent of normal, hemophilia A's most severe form, have a high risk of spontaneous hemorrhage resulting in joint, soft tissue, and organ morbidity and a high rate of mortality. Current therapies are not uniformly effective because of the requirement of periodic infusion of FVIII. Minimal beneficial levels of FVIII of 2 to 5 percent of the normal level produce significant benefits, changing hemophilia A from a severe bleeding disorder to one that is moderate or mild. Patients generally treat themselves with FVIII after a bleeding episode occurs, a process termed "demand treatment." Some prophylactic treatment is used for younger patients, with frequent injections of FVIII concentrates that are not completely preventive because continuous levels of FVIII cannot be maintained. GTR may provide a mechanism by which continuous levels of FVIII could be achieved.

The vector used in these studies is a minimal (gutted) adenoviral vector with no viral coding sequences (miniAd); it encodes the full-length complementary DNA (cDNA) for human FVIII (hFVIII). The vector has been optimized for gene expression and stability in the liver by the presence of a human albumin promoter and genomic fragments from the albumin gene, which promote liver-specific expression and stability. The vector is of high purity, is replication incompetent, and is an adenovirus helper-free production. Expression of therapeutic levels of FVIII has been sustained in mice; a correction of phenotype in hemophilic mice has also been seen. This gutted adenoviral vector shows improved safety profile compared with the earlier generation of adenoviral vectors.

Dr. Wei-Wei Zhang, GenStar Therapeutics Corporation/UroGen Corporation

Preclinical studies show sustained high-level gene expression in hemophilic and nonhemophilic mice, with restoration of normal clotting activity in the hemophilic mice. This vector displays liver tropism and DNA persistence. Minimal toxicity was exhibited in animal models. A Phase IA trial with two cohorts of three adult patients each, is proposed, using single intravenous (IV) dosing.

The goal of this study is to develop a safe and effective vector. MiniAdFVIII vector (minimum adenoviral vector for Factor VIII) contains no viral coding sequences; other terms for this vector include helper-dependent, larger capacity, gutted, or minimal. The miniAdFVIII vector is an adenovirus-based vector designed to restore production of hFVIII by delivering the entire FVIII cDNA to somatic cells. Researchers anticipate that the vector will not express adenoviral antigens *in vivo*, minimizing potential immune responses and resulting in long-term persistence of the vector and expression of the transgene. Nonclinical pharmacology studies indicate that physiological levels of hFVIII were produced *in vivo*, and these levels persisted for an extended period of time, resulting in phenotypic correction in hemophilic mice.

The objective of this Phase I study is to evaluate, through dose escalation in defined increments, the safety of IV infusion of miniAdFVIII vector in severe hemophilia A patients without inhibitors. Additional study objectives are to (1) evaluate the ability of IV infusion to produce circulating, functional levels of FVIII; (2) evaluate this therapy using the frequency and severity of bleeding events; (3) evaluate immunologic responses; and (4) determine the functional FVIII expression profile. The proposed study consists of a 7-day screening phase, a 1-day treatment phase, a 12-week posttreatment phase, and a

2-year followup phase. Six patients will be enrolled in two cohorts, with three patients per cohort. Cohorts will be separated by at least 2 weeks.

A transient decrease in platelet counts at day 3 postinjection was seen in the highest dose group in mice; mild alanine transaminase (ALT) elevation and minimal cell infiltration in the liver were also seen in this group. Antivector and

hFVIII antibodies were detected in all treated mouse groups. No other significant toxicities were observed. A review of vector biodistribution and persistence in mice—by polymerase chain reaction (PCR) assay—indicated that more than 80 percent of the vector was localized to the liver. Vector DNA persisted in the mouse liver cells in an episomal form over the course of 1 year.

Dr. White

Dr. White stated the investigators' belief that this trial should be considered largely on the basis of the improved safety profile and because the vector is tropic to the liver (where FVIII is made). The trial will consist of two doses: $1.4x10^{10}$ and $4.3x10^{10}$ viral particles per kilogram (p/kg). Each dose will be given to three patients. Route of administration is by peripheral IV infusion. The levels of virus to be administered are two orders of magnitude below the therapeutic levels seen in the mouse, but investigators expect the vector will be more efficient in humans because of the use of human albumin promoter.

Inclusion criteria consist of patients with severe hemophilia A, FVIII levels of less than 1 percent of normal, age older than 18 years, greater than 150 days exposure to hFVIII concentrates of any type, and normal aspartate transaminase (AST) levels. Patients will be excluded from study participation if they have elevated ALT levels; clinically significa cardiovascular, autoimmune, and pulmonary disease; prothrombin time more than 2 seconds above control; a platelet count of less than 100,000; or a history or the presence of an FVIII inhibitor.

Study safety parameters will include hematology, chemistry, urinalysis, and physical examination; investigators are particularly interested in immunogenicity, FVIII antibodies, and antiadenoviral antibodies. Although this is a toxicity study, investigators will measure FVIII levels, quantify bleeding events, and examine the clearance of vector and FVIII levels.

Two stopping rules, both related to the liver, are built into this study: (1) any two patients with ALT that increases to two times the upper limit of normal or who have any grade 2 toxicity or (2) a single patient developing a FVIII inhibitor or a grade 3 toxicity. ADSMB has been organized to regularly review study data and will submit reports to participating IRBs.

Dr. Jeffrey S. Chamberlain, University of Michigan, *Ad Hoc* Consultant

Dr. Chamberlain stated that available data suggest that the gutted adenovirus system has great potential, displaying significantly reduced toxicity and greatly improved safety compared with first- and second-generation adenoviral vectors. However, it is critical to consider what goes into this system, how the virus is grown, and what sort of quality-control assays are used. Dr. Chamberlain briefly reviewed the basic features of gutted adenoviral vectors.

The helper-dependent adenovirus system is composed of a DNA that contains an origin of replication of adenovirus and a packaging signal, together with a therapeutic gene. Since it is not a replication competent virus, it can be grown only in the presence of a helper (ancillary) virus that provides all of the necessary proteins for replication. Genetic manipulations can be made of the ratio of gutted-to-helper virus. The gutted virus system is a little more difficult to grow and produce than other adenoviral vectors, so laboratories must go through a variety of serial passages. After a number of serial passages, the titer of the gutted virus rises considerably, whereas the titer of the helper virus general remains constant, and some rearranged products may be detected. Earlier vectors require only one round of growth and replication, whereas the gutted adenovirus requires multiple rounds of replication with some potential to lead to rearrangement of these viruses. Two other serious issues are how much of the helper virus is present in the preparations and the nature of that helper virus.

Dr. Chamberlain discussed several safety issues. The gutted virus has no viral genes and is therefore incapable of vir

gene expression. Tissue-specific expression of the transgene within the gutted virus appears to be an important safety consideration; equally important is the nature of the helper virus—the percentage of contamination and its safety profile—and the relative stability of both the gutted and helper viruses. The toxicity of different types of gutted vecto needs assessment, since not all gutted vectors are the same. Even though the gutted vectors have no viral genes, they are encapsidated in an adenoviral coat, which means the potential of high-dose administration of adenoviral capsid must be considered even in the absence of adenoviral genes. A variety of serial passages is needed to obtain high enough titers of these vectors to make them useful, so the issue of what constitutes a seed stock needs to be defined, and the level of quality control to verify the integrity of that seed stock also needs definition. Because additional rounds of serial passages are needed to make seed stock into clinical-grade vector preparations, it is critical to ensure that there have not been subsequent rearrangements of the vector in those final rounds of growth.

Some laboratories have had difficulty growing these vectors compared with conventional adenoviral vectors, so it is unclear whether production of these viruses can be scaled up and whether an individual laboratory will be able to prepare enough of this vector to achieve a therapeutic dose.

Dr. Ando, Co-Chair

Dr. Ando provided an overview of and the issues embedded in this protocol. Key issues are preclinical toxicity, preclinical efficacy, dose, and the immune response of the adenovirus. Preclinical issues include the vector encoding hFVIII being an adenoviral vector deleted of all viral gene sequences and its delivery systemically by the IV route. D Ando also discussed other issues, including whether this vector has an acceptable toxicity profile for the patient population, how the preclinical and prior clinical findings should be addressed in the consent form, the approach to dose escalation if no toxicities are noted in the first two doses, and whether and how to determine an absolute limit th should be set on the maximum amount of vector administered.

Dr. Aguilar-Cordova, Co-Chair

Dr. Aguilar-Cordova provided a general discussion about the difference between this helper-dependent vector and earlier generation vectors. Significant databases exist for first-generation vectors. Gutted vectors look the same on th outside as the first-generation vectors but are quite different inside. Dr. Aguilar-Cordova discussed the following issues:

- Vector-disease match. Vector features include the potential for integration, acute and chronic immunogenicity, target tissue, and expression/duration. Disease features include acute vs. chronic, fatal vs. nonfatal, required levels of expression, monogenic vs. polygenic, required location of expression, and disease-affected tissues.

- Product-specific issues. Existing adenoviral vector databases are likely to be instructive because distribution is unlikely to be different. Duration of expression or the presence of the vector is likely to differ and should be clearly evaluated for each protocol. Because of the increased size of helper-dependent vectors, there may be more propensity to recombination, and thus, genome rearrangements could occur; as a result, there is a need to determine what levels would be acceptable.

- Building an acceptable safety package for clinical trials. Data on distribution are already available, using the database from first-generation adenoviral vectors. The possibility of the existence of antiadenoviral antibodies is crucial for clinical trial participants, since a stronger antibody response may be elicited on second administration of the vector. Regarding liver toxicity or thrombocytopenia, if the disease already has significant liver toxicity, it is important to know whether this vector will enhance that disease status. Other safety issues include stable integration, rearrangements *in vivo*, choice of injection site, and potential for threshold effects (variability between studies and among patients, as discussed at the

December 1999 RAC meeting).

• Dose-escalation schemes. Issues include how dose escalation should be designed; whether animals can adequately predict what will happen in humans; first-dose prevention of future dosing (a critical issue if starting well below the predicted therapeutic dose), which may mean that patients are prevented from receiving a possibly therapeutic dose; threshold effect; and whether predictors of susceptibility to toxic effects exist.

• Generic variables. Issues include what is being injected (quantity, quality, structure, and genetic content); where it is being injected (species and site); when it is given (patient age and health status); and how it is given (time, volume, and carrier).

Dr. Ann M. Pilaro, FDA

Dr. Pilaro discussed additional information contained in the IND package that supports the FDA's decision about the doses chosen for this clinical trial. No observable adverse effect level (NOAEL) is the highest dose given to animals in the absence of detectable toxicities. For example, the difference between the starting dose for the clinic and the higher dose at which no toxicity was seen in mice was 114- to 285-fold. Another study reviewed by the FDA involved cotton rat systemic administration; the NOAEL in this study was $1x10^{13}$ vector p/kg, producing a safety factor of 700-fold greater than the starting dose for the clinic. The FDA believes, therefore, that the safety of this novel vector system is supported by the toxicity data. Another study, using dogs, showed no evidence of toxicity; however, the pharmacologic activity was not the same as that seen in the mouse.

Mouse and dog pharmacology studies do not show effective gene transfer below $1x10^{12}$ vector p/kg. However, the no-effect doses from the animal studies show no toxicities at doses of up to $4x10^{13}$ vector p/kg. Two doses are proposed for this study, both of which are 100- to 200-fold lower than the NOAEL dose in the mouse and 50-fold lower than the dose at which pharmacologic activity is seen. The dose at which effective gene transfer occurs in animal studies is twofold to tenfold higher than that received by Jesse Gelsinger. However, the safety data in this case do support the use of these higher doses.

RAC Questions and Comments

Dr. Aguilar-Cordova queried the investigators about the stability of the vector system and how often the investigators have seen rearrangements in gutted viruses. Dr. Chamberlain responded that the experiences from several laboratories including his, suggest that every vector is a little different in terms of stability; some vectors grow repeatedly without any rearrangements, whereas others rearrange readily. Both Dr. Chamberlain and Dr. Zhang responded further that Southern blot analysis will be used to increase the sensitivity several hundredfold and that enzyme digestion Southern blot as well as some fragments by PCR, have demonstrated the integrity of the vector. No vector rearrangements have been observed so far.

Dr. Mickelson wondered, since some toxicities were not seen (for first-generation vectors) until high doses were administered in primates, whether animal models are appropriate, in part because the distribution for receptors is different in humans even from other primates. Dr. Noguchi responded that the earlier animal studies may not have shown as much toxicity, but those studies also used a small number of vector particles. Dr. Pilaro indicated that the number of receptors in the mouse liver for adenovirus is much higher than in human or other animal models. Therefore, the mouse model tends to overpredict some of the toxicities and also provides a worst-case scenario for getting the maximal amount of adenovirus into liver cells.

Dr. Gordon asked whether, if enough receptor is not present in the liver to take the virus out of the bloodstream and i

therefore distributed widely throughout the body, the virus could overwhelm neutralizing antibodies, thus producing another toxicity (in addition to hepatotoxicity) that might be unique to humans. Dr. Pilaro responded that toxicity studies are designed to examine a systemic panel of markers, not liver toxicity only. With adenoviruses, the two majo toxicities are transaminitis in the liver and platelet consumption; these toxicities seem consistent for first-generation, second-generation, the E1/E4-deleted, and also gutted vectors. These warning flags should be looked for in the clinical trial.

Dr. Ando asked how the informed consent issue should be approached with patients. Dr. White responded that the benefit-toxicity ratio of this gutted adenovirus is improved compared with nongutted adenovirus, so that giving less vector will produce the same clinical effect—benefiting the patient by producing less toxicity. It is important to emphasize with patients the liver toxicity that has been seen with nongutted adenoviruses. Other informed consent issues with patients include possible pulmonary and hematological toxicities, but the investigators hope that the ratio those toxicities relative to the benefit will be improved.

Dr. Ando also asked what will guide the investigators in determining dose escalation if the vector is determined safe but no effect is seen. Dr. White emphasized that investigators will emphasize to patients that, by participating in this study, they will not be candidates for another dose later in the study nor will they be candidates for some interval for other gene transfer trials. The trial will start at a low dose and include a small increment in dose; the investigators would like to be cautious in their approach to dose escalation, to determine whether this vector is safe and effective.

Given the toxicity profile with respect to liver abnormalities and platelet abnormalities, Dr. Ando wondered how hemophilia clinicians and patients feel about the use of these vectors. Dr. White responded that the advantage of usin this vector in patients with hemophilia is that a small dose of vector has the potential for benefit, because only a smal level of additional FVIII is needed for patients to receive a measurable benefit. Most patients who are candidates for this trial are hepatitis C virus (HCV) positive and have abnormal liver function tests. However, the AST changes that have been seen in the animal models are small and well within normal limits; therefore, the investigators will start wi only those patients who have normal AST levels. Patients who have transient thrombocytopenia will receive FVIII during this short period, as is normally done, so that they will not be at increased risk.

Dr. Friedmann raised the question of whether the trial would convert some of the noninhibitor patients to inhibitor patients by exposing them to an adenoviral vector, thereby making them less responsive to traditional therapy. Dr. White answered that this concern is real. Currently, no method exists for predicting which patients are likely to be at risk for this conversion. If a patient does develop an inhibitor, the question will be whether it is related to the vector o whether it occurred by a mechanism independent of the vector and inherent to the disease. In the three ongoing clinical trials of about 20 patients, there have been no reports of inhibitor formation using retroviral, adeno-associated viral (AAV), and *ex vivo* nonviral vectors.

Dr. Ando noted that the mechanism of the toxicity—whether it is the actual particle or the receptor-mediated endocytosis—is unclear at present. Given that lack of clarity, he expressed concern about the adequacy of the safety factors—the preclinical studies, the informed consent, and the careful dose escalation. Dr. Chamberlain agreed that there are still some unknowns about how adenovirus gets into cells. If enough virus is added to a plate of cells, an obvious cytopathic effect occurs that is not seen at lower doses. The injection of adenovirus involves a threshold of transduction: At lower doses no expression is seen, but when a certain dose level is reached, a great deal of expressio is seen. This effect argues against a simple receptor-mediated uptake, but no data address this issue directly.

Dr. Ando also queried Dr. Noguchi about whether damage must occur to see expression and whether any scientific data show linkage between the two. Dr. Noguchi mentioned one study, from 6 or 7 years ago, using a cystic fibrosis mouse, which skirted but did not directly answer the question of whether there is any receptor-mediated endocytosis. Dr. Gordon explained that some experiments in his laboratory show, preliminarily, the ability to get adenoviruses int cells while completely bypassing the endocytic mechanism, thus producing no Lac-Z expression. Dr. Chamberlain

explained that recent studies indicate that the epithelial cells of the lung and the trachea do not express the coxsackievirus and adenovirus receptor for adenovirus, but it is expressed on the basal side of the cells.

Ms. King asked whether it is fair to ask subjects to participate altruistically in this kind of clinical trial, when considerable consequences could occur, that is, whether human Phase I trials are likely to reveal information that is n obtainable from animal models and other preclinical experiments. Dr. White responded to this ethics-related questior by stating emphatically the importance of the discussion point with patients about how participation in this trial will preclude their participation in other gene transfer clinical trials for the duration of this study. He also answered that h believes it is fair to ask a patient to participate in such trials but that the patient must understand the risks and potenti exclusion issues. Dr. Juengst added that it is a judgment point about whether it is time to seek out a group of (altruisti volunteers. He wondered whether there are other strategies for additional preliminary research that would reduce the risk to human volunteers before proceeding to the clinical trial. If no other option is left except to study the human experience, then Dr. Juengst believes it is appropriate to search out human volunteers. Dr. Noguchi added that, if the field is confident enough from a scientific basis and if available clinical data indicate that this gutted vector may represent an increment in safety, then it is appropriate to go forward with clinical trials.

Dr. Breakefield queried whether hemophilia is the appropriate disease with which to study the gutted adenoviral vector, given that patients likely will have some liver damage before the trial begins and the risk of patients forming inhibitors to FVIII. Dr. Gordon Bray, Baxter, explained that inhibitors are a well-recognized complication of conventional hemophilia replacement therapy. This study was designed to select patients who are inherently at low risk of inhibitor development, because they will have had extensive prior exposure to exogenous FVIII infusions. The risk of inhibitor development is greatest at the earliest stages of substitution therapy so that, once a patient is beyond 150 days of exposure to FVIII, the risk of inhibitor development declines dramatically. Concerns expressed about inhibitor formation will exist with most gene therapy protocols, not just with this proposed trial.

Dr. Sobol (UroGen Corporation) stated his belief that clinical data are available and compelling. Data from several laboratories show the significantly improved safety profile of the gutted vector. On the basis of strong data, this vecto is ready for testing in human subjects.

Public Comment/Dr. Richard Snyder, Harvard Medical School and Children's Hospital, Boston

Dr. Snyder stated his hope that investigators will examine vector purity issues, including contaminating FVIII in the vector preparation that was expressed by the vector *in vitro* during vector production. Clotting factors can become denatured or fractured, which could be a source for inducing inhibitor formation..

Discussion Summary

Dr. Mickelson summarized the three main unresolved issues: (1) whether the deletion of the adenoviral structural proteins and the toxicity associated with synthesis of those proteins intracellularly are the main components of adenoviral toxicity and destruction of transduced cells; (2) whether the amount of toxicity that remains in the envelope of the helper-dependent adenovirus provides a high enough barrier to ask for more clinical data or whether available data are sufficient; and (3) whether the safety profile is adequate to address the two prior issues.

Other unresolved issues noted by Dr. Mickelson were as follows: how infinitely mutable is a vector, when does a vector cease to become an adenovirus, and use of a type of vector that may have residual toxicity associated in patien with at least some liver damage.

Dr. Aguilar-Cordova summarized the issues discussed as follows:

- Genetic stability

• Testing multiple sequential preparations with a high-sensitivity assay

• Helper-vector contamination and determining sensitivity of the assay and the effect of contamination on study design, expression, duration, andimmunogenicity

• Stability and equivalence of preclinical and clinical lots

• Stability and potency after transport to the study site

• Dose-escalation scheme. Safety as a first concern and the potential for future preclusion from standard of care

• Vector-disease match. Whether this vector is significantly improved in toxicity and duration profiles to warrant further clinical studies

• Consideration of the risk-benefit ratio

IV. Discussion of Human Gene Transfer Protocols #9911-358 and #9911-359:*A Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12cDNA by Intratumoral Injection in Patients With Metastatic Breast Cancer to the Liver* and ***A Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients With Primary or Metastatic Malignant Tumors in the Liver***

Principal Investigators: Dr. Max W. Sung, Mount Sinai School of Medicine

Dr. Savio L.C. Woo, Mount Sinai School of Medicine

RAC Reviewers: Drs. Ando, Chow, and Juengst

Ad Hoc Consultant: Dr. Robert Warren, University of California, San Francisco (written review)

The principal investigators provided a 15-minute presentation of their protocol, the reviewers discussed their concern (with time allotted for responses), and the RAC and the public presented additional questions.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were either unresolved or novel and that the protocol warranted public discussion. These issues included: 1) safety and toxicity issues surrounding adenoviral vectors, particularly when the vectors are administered directly into the liver; 2) the need for data on biodistribution from animal models of the disease condition under study; and 3) a concern about the safety of the dose escalation plan to increase by half log increments to a maximum dose of 1×10^{14} virus particles.

Drs. Ando, Chow, and Juengst submitted written reviews, to which the investigators responded in writing. Major concerns expressed in the written reviews included tissue biodistribution of adenoviral vector by PCR following intratumoral (IT) injection in tumor-bearing mice; expression profile of the transgene herpes simplex virus thymidine kinase (HSV-tk) following IT injection in tumor-bearing mice by radiolabelled FIAU (2'-fluoro-1-a-D-arabinofuranosyl-5-iodo-uracil) imaging; results of previous clinical studies; safeguarding the risk of vector leakage; dose assessment; and use of corticosteroids to ameliorate the adverse effects of the recombinant

cytokine protein.

Protocol Summary

Interleukin-12 (IL-12) is a protein product of monocytes and macrophages that has been shown in animal studies to produce tumor regression by enhancing immune responses directed against tumor cells. The recombinant IL-12 protein has been administered to patients with advanced cancer and has been found to be toxic at higher doses, with limited antitumor efficacy.

The researchers have shown in mice bearing established tumors in their livers that gene transfer by IT injection of an adenoviral vector expressing murine interleukin-12 (AdV-mIL-12) was effective in producing tumor regression and survival prolongation, with 20 to 40 percent of treated animals alive at 160 days compared with control animals that died by 75 days. The treatment was also well tolerated without serious adverse effects at therapeutically effective doses of the vector. When AdV-mIL-12 was administered at higher doses, toxicities were seen that were similar to those of the recombinant IL-12 protein.

Investigators have translated these preclinical findings into two Phase I trials. Both trials aim to evaluate the safety of adenoviral vector expressing human IL-12 (AdV-hIL-12) when administered by IT injection in patients with liver tumors. One trial will study patients with metastatic breast cancer to the liver, and the other will evaluate patients with metastatic nonbreast or primary malignant tumors in the liver. The IT injection is performed by percutaneous insertion of up to three thin needles through the skin into one liver tumor under ultrasound guidance. The dose of AdV-hIL-12 will be escalated in half-log increments in seven cohort levels from $1x10^{8}$ to $1x10^{12}$ plaque-forming units, with three patients per dose-level cohort. The starting dose is four logs of magnitude below the equivalent dose by body weight that has been shown to be well tolerated in mice. Investigators will also collect data on the effectiveness of the treatment in producing tumor regression and in inducing immune responses.

Clinical grade AdV-hIL-12 has been produced for use in the proposed clinical trials by the University of Pennsylvania Institute for Human Gene Therapy. The trial in metastatic breast cancer is sponsored by the U.S. Army Medical Research Acquisition Activity, and the trial in patients with metastatic nonbreast or primary cancers in the liver is sponsored by the Mount Sinai School of Medicine.

RAC Discussion

Dr. Juengst summarized his review as comments oriented toward the framing of the informed consent form; the changes made by the investigators addressed his concerns.

Dr. Ando's review focused on the potential synergistic effect of adenoviral toxicity and IL-12 toxicity on the basis of two issues—dose escalation and early clinical involvement of hIL-12 as a protein. He suggested that, as dose escalation occurs in this trial, careful monitoring of the cytokine levels should occur; once changes in cytokine levels are seen, investigators should increase patient monitoring. The investigators were careful to monitor the cytokine levels in the mouse studies.

Dr. Warren offered his review in writing, which Dr. Ando summarized. Dr. Warren suggested that the original two groups (metastatic breast cancer and primary hepatic cancer) should be regrouped by assigning the breast cancer and metastatic patients to one group and the hepatoma patients to the other; patients in the former group would be more similar to each other and more likely have normal livers. Dr. Warren added that patients should be offered liver resection if they are candidates. In the studies that Dr. Warren performed, Swan-Ganz catheter monitoring at a specific dose level was helpful; he offered to review this procedure with the investigators to determine its suitability in this tr

Dr. Chow was not present to discuss her review.

RAC Questions and Comments

Dr. Breakefield was concerned about what happens to the vector when it is injected intratumorally. Since the adenoviral vector expresses IL-12, there is a potential for leakage, since IL-12 can produce a vascular leak syndrome and the vector could be disseminated throughout the body as a result. Dr. Woo explained that vector distribution is a definite concern; however, the probability that vascular leak will result from recombinant IL-12 after vector delivery low, primarily because the transgene product is not present when the virus is injected.

Regarding vector distribution, Dr. Sung indicated that no vector DNA was detected in the kidneys, heart, lungs, or ovaries of injected animals. Some presence was observed in the liver (less than 100 copies), and presence was variab in the spleen. Studies support the notion that IT injection does not produce a significant vascular leak syndrome that would disseminate the vector.

In response to Dr. Warren's comments about hepatocellular carcinoma and coexisting liver disease, Dr. Sung stated that the eligibility criteria are strict and that the assessment of liver dysfunction is based on the eligibility criteria. Primary liver cancer patients will be removed from the second protocol to become a third protocol addressing primar liver cancer, so that toxicity can be examined in this group of patients.

Regarding monitoring of patients and the frequency of cytokine measurements, Dr. Ando asked whether IL-12 and gamma interferon peaks were taken into account. Dr. Sung indicated that patients will be monitored starting the day after vector injection, because investigators are aware that the inflammation syndrome can occur rapidly after injectio They will use a technique to do the ELISAs on minute amounts of blood so as not to be a major drain on the patient.

Dr. Breakefield requested an explanation of the second peak of IL-12 and asked whether it is a second burst of vector production. Dr. Woo theorized that the first peak of activity is the transgene product. The second peak of activity is endogenous IL-12 expression from the macrophages that were subsequently recruited to the tumor site.

Dr. Aguilar-Cordova requested an explanation of the dose-escalation scheme and the highest dose level. Dr. Sung explained that the investigators used body weight as a conversion factor. The starting dose for the clinical trial is fou logs below the maximum nontoxic dose in animals. Dr. Ellis asked whether the subjects receiving the higher doses will know what dose they are getting, to which Dr. Sung responded positively. Investigators revised the dose-escalation scheme, incorporating arithmetic increments at the higher doses. The highest dose has been deleted, until more data are accumulated, to ensure safety; the revised highest dose is $3x10^{13}$ p/kg.

Regarding the issue of consenting patients and whether patients are fully informed about potential toxicities, the investigators noted that revisions were made to the Informed Consent form to include information on toxicities from preclinical animal studies and the recent death of a participant in a gene transfer trial. Language changes include replacing "study treatment" with "study procedure" and eliminating discussion about the potential for symptom relief after study treatment. The most recent consent form was distributed; that revised form was approved by the IRB on March 7, 2000.

Public Comment

None.

Committee Motion

To address issues raised by Dr. Warren, the committee has requested a written response from the investigators

outlining their response to the recommendations listed below:

> Due to a concern about concurrent chronic liver disease in patients with primary liver tumors, the study design should be modified. The protocols should enroll only subjects with metastatic tumors. As the investigators have agreed at the meeting, a separate third protocol should be developed for subjects with primary liver tumors.
>
> Liver resection is an alternative treatment for patients with solitary primary liver tumors, and subjects should be informed through the consent process and document of this alternative treatment.
>
> Due to concerns about the hemodynamic stability of patients enrolled in the high dose cohorts, the investigators should consider hemodynamic monitoring of such patients. For this purpose the investigators may wish to consult with Dr. Warren, University of California, San Francisco, regarding the use of hemodynamic monitoring catheters such as a Swan-Ganz catheter.

The RAC passed the motion to include the three specific recommendations listed above in a letter to the investigators by a vote of 9 in favor, 0 opposed, and no abstentions.

> **V. Discussion of Human Gene Transfer Protocol #9912-366:** ***A Phase III, Multicenter, Open-Label, Randomized Study To Compare the Overall Survival and Safety of Biweekly Intratumoral Administration of RPR/INGN 201 vs. Weekly Methotrexate in 240 Patients With Refractory Squamous Cell Carcinoma of the Head and Neck***

Principal Investigator: Dr. John T. Hamm, University of Louisville

Sponsor: Dr. Angus Grant, Aventis Pharmaceuticals - Gencell Division

RAC Reviewers: Drs. Friedmann and Gordon and Ms. Levi-Pearl

The principal investigators provided a 15-minute presentation of their protocol, the reviewers discussed their concern (with time allotted for responses), and the RAC and the public presented additional questions. This protocol is the fir Phase III study the RAC has reviewed.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were eithe unresolved or novel and that the protocol warranted public discussion. These issues included: 1) a discussion of the *in vivo* fate of the adenoviral vector after intratumoral injection; 2) a discussion of any evidence of cytokine release into the circulation; and 3) the benefit of public discussion of vector biodistribution data and autopsy findings of patients enrolled in the ongoing earlier phase clinical trials.

Drs. Friedmann and Gordon and Ms. Levi-Pearl submitted written reviews, to which the investigators responded in writing. Major concerns expressed in the written reviews included evidence of positive results in the Phase II trial, clarification of the dosing schedule, whether patients with refractory squamous cell carcinoma of the head and neck (SCCHN) are normally treated with methotrexate, the *in vivo* fate of the adenoviral vector after IT injection, and several specific Informed Consent form issues.

Protocol Summary

SCCHN is diagnosed in 40,000 new cases each year. The average survival is 3 to 5 months, with a higher incidence of occurrence in lower socioeconomic males and African Americans. Recurrences occur mostly to the head and neck and are not systemic. Therapeutic options are limited; salvage surgery or reirradiation are rarely offered. Chemotherapy is the standard of treatment and is effective but relatively toxic.

Sixty centers are planned for this multinational Phase III, multicenter, open-label, randomized study. The primary objective is to compare the overall survival in patients receiving RPR/INGN 201 with patients receiving methotrexate. RPR/INGN 201 is a non-replicating adenoviral vector which encodes a wild type p53 tumor suppressor gene driven by the cytomegalovirus promoter/enhancer. Secondary objectives are to compare the locoregional time to disease progression, objective response rate, tumor growth control rate, overall time to disease progression; to compare the impact on quality of life of RPR/INGN 201 vs. methotrexate; to evaluate the effectiveness of RPR/INGN 201 with methotrexate in reducing cancer morbidity; and to evaluate the safety and tolerability of IT administration of RPR/INGN 201 vs. IV methotrexate. Patients will be randomized to one of two treatment arms: RPR/INGN 201 on days 1 and 3 of each week and methotrexate once every 7 days. The total number of patients planned is 240, with 120 per treatment group. Inclusion criteria include recurrent or progressive primary SCCHN confirmed at least by cytology, ineligibility for resection, prior treatment with a minimum of standard method radiation or medically ineligible to receive such therapy, failure of at least one chemotherapy regimen or medical ineligibility to receive the therapies, absence of central nervous system (CNS) metastasis, age 18 years or older, and all disease located in the head and neck region accessible to IT injections.

As the reference therapy, methotrexate will be administered initially at 40 mg/m^2 IV bolus once every 7 days for 3 weeks; subsequent doses may be escalated by 10 mg/m^2 increments after the first phase, up to 50 mg/m^2 if deemed clinically appropriate. In the event of toxicity attributed to methotrexate, the dose may be reduced by 10 mg/m^2. If a patient experiences significant toxicity, retreatment by methotrexate may be delayed for a maximum of 2 weeks. In the absence of recovery either to the baseline value for preexisting sign and symptom toxicity equal to or less than grade 1, the patient will be removed from treatment.

The planned duration of this study is 34 months, with a planned enrollment duration of 22 months. The duration of one treatment phase is 21 days. Patients will be treated for 27 weeks (9 treatment phases) unless there is documented locoregional disease progression or unacceptable AEs. Treatment beyond 9 phases, in patients with documented evidence of absent locoregional progression, will be considered on a patient-by-patient basis for a maximum of 17 phases. All patients will have a short-term followup visit 28 days from completion of the last treatment phase. Long-term followup will continue every 6 weeks until death or end of study. Survival data, cancer morbidity data, and quality of life will be collected for all patients every 6 weeks until death or end of study.

Efficacy will be evaluated by overall survival (defined as the amount of time elapsed from the date of randomization the date of death) and locoregional disease progression and tumor growth. This study is designed and powered to establish patient benefit, enrolling the same patients who participated in the Phase II study. Secondary endpoints include additional biodistribution tests.

RAC Discussion

Dr. Friedmann summarized his written review. He wanted to know whether the investigators believed there was any reason to review any existing evidence for systemic release of cytokines after local delivery of p53 into a tumor. Dr. Friedmann was not convinced that p53 is as innocuous a gene as the response from Aventis indicated. Dr. Antoine Yver, senior director at Aventis, responded that no animal or human data currently support any profiling of cytokine release, but the investigators consider this question critical. Extended safety assessments have been done on hundreds

of patients in prior Phase I and Phase II studies.

Dr. Gordon began the summary of his review by relating a situation from his medical internship when he had a patie with advanced head and neck cancer, stating that the impression this patient left with him was that anything that can be done for these patients should be tried. He was concerned that methotrexate would possibly get to cells that a direct injection could not reach; the presentation at this meeting addressed this concern adequately—methotrexate is not prolonging the lives of these patients. Dr. Gordon stated his belief that p53 typing or grading gene mutation should be done. Dr. Hamm responded that all patients will have tissue obtained for p53 typing prior to starting the study. Methotrexate, as a control treatment for patients with refractory SCCHN, is an established, palliative therapy, chosen as a control for patients with refractory disease in two other studies.

Ms. Levi-Pearl presented her review by thanking the investigators for responding so completely to her comments about the Informed Consent document. She reiterated her concern for Phase I trials that convey the idea of "treatmen in these safety-only studies and stated that, should this Phase III trial prolong the lives of SCCHN sufferers, the term "gene therapy" (as opposed to "gene transfer") could be used appropriately to describe this procedure.

RAC Questions and Comments

Dr. Aguilar-Cordova queried whether data exist on the expression levels of p53 after injection. Dr. Yver responded that in the Phase I trial, there was proof of expression after the first injection and also after the third injection, by reverse transcriptase-PCR (RT-PCR), protein expression, downstream molecular events of p21 expression, and evidence of apoptosis induction compared with baseline.

Dr. Aguilar-Cordova also asked a question about biodistribution: whether the investigators see different levels of duration of plasma vector after different injections. Dr. Yver responded that serum plasma levels were detected in Phase II. A pattern of expression does not vary from month to month, despite the fact that antibodies are present and the virus is being injected into a solid-mass tumor.

In response to questions about the integrated safety assessment, the investigators stated that no treatment-related deat occurred. The two most common related AEs were fever (for a few hours after injection) and injection site pain (40 percent of patients). Generalized pain, nausea, asthenia, and so forth are usually seen in patients with cancer, whethe or not they are on treatment.

Ms. King was concerned that the consent form stated too optimistically that participation in the methotrexate arm of this study "may result in shrinkage of your tumor which may decrease cancer associated symptoms or may prolong life." Dr. Hamm responded that this is a standard IRB-requested inclusion to preclude making the standard therapy arm of the study appear worse than the treatment arm. Ms. King further suggested that the consent form should lay o clearly the choices for subjects because, unlike Phase I studies in which subjects have no right to expect positive results, subjects participating in Phase III studies may reasonably expect positive results from their participation.

Dr. Noguchi clarified that the FDA has already met with the company. A Phase III study is a contract between the FDA and the company; eligibility for approval as a therapeutic product will occur if the product is demonstrated to b effective and the manufacturing and other issues are dealt with satisfactorily. This company is willing to present its data and answer questions, but RAC review of a Phase III trial should be placed in a different category, as informatio for the public. Phase III studies answer the question of effectiveness, compared with an appropriate control, and whether patients benefit. Dr. Patricia Keegan, FDA, further explained that, in all clinical trials, the actual mechanism of action of the drug may not be completely understood, but if the drug is effective and the toxicity profile is acceptable for the disease, the FDA will approve the drug because it helps people: "Effectiveness always trumps science."

Committee Motion

Dr. Mickelson thanked the investigators, stating that the RAC rarely has a chance to look at mature phase III protocols, such as this one, that are supported by a strong body of data. She stated that a letter will be sent from the RAC thanking the investigators for presenting their advanced data. The sense of the RAC was that the letter should include a request for a follow-up presentation to the committee as the study progresses. Data from the large number o patients from this study will provide useful information to the field.

A motion for the above recommendation was made by Dr. Aguilar-Cordova and seconded by Ms. King, and the RAC passed the motion by a vote of 9 in favor, 0 opposed, and no abstentions.

Dr. Hamm explained that the investigators were asked not to enroll participants until after this RAC meeting, so he requested that the RAC allow enrollment. Dr. Mickelson, for the RAC, stated the RAC's assent for enrollment.

VI. Minutes of the December 8-10, 1999, Meeting/Dr. Aguilar-Cordova and Ms. Levi-Pearl

Dr. Aguilar-Cordova and Ms. Levi-Pearl both stated that the minutes appeared accurate and were well written. The RAC approved a motion made by Dr. Gordon and seconded by Dr. Greenblatt to accept the minutes of December 8-10, 1999, RAC meeting (with the incorporation of minor editorial changes) by a vote of 9 in favor, 0 opposed, and no abstentions.

VII. Data Management/Dr. Greenblatt

Dr. Greenblatt reported that a total of 389 gene transfer protocols have been submitted to the OBA; 32 new protocols were submitted to the OBA since the last reporting period, 22 of which were exempted from full RAC review. Originally, 10 protocols were to be reviewed at this March 2000 RAC meeting; however, 2 were withdrawn.

Review of the protocols indicates that 37 are for gene marking, 350 are for gene therapy, and 2 are for normal volunteers. Breakdown of the gene therapy protocols indicates that the largest category is for cancer (234 protocols); 49 protocols are for monogenic diseases, 35 protocols are for other diseases such as rheumatoid arthritis and coronary artery disease, and 32 protocols are for infectious diseases, all but one of which were for the human immunodeficien virus (HIV).

There were 27 amendments reported since the last reporting period, all of which were relatively minor amendments such as adding new sites or investigators, clarification of eligibility requirements, changes to the consent form, updat on the status of the protocols, typographical errors, and increase or decrease of the proposed dose administered to patients.

From January 1 to February 15, 2000, the OBA received 301 AE reports; 278 were initial reports, and 23 were followup reports. Thirty-five were considered serious (possibly associated and unexpected), and only one AE report needs to be discussed at this meeting—a followup report for protocol #9082-233, a Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid for Allovectin-7 as an Immunotherapeutic Agent for Patients in Stage III or IV Melanoma With No Treatment Alternatives (being conducted in Arkansas). In this study, a patient undergoing treatment for metastatic melanoma with lesions in the lungs and enlarged nodes in the groin developed severe ascites and gastrointestinal bleeding on July 15, 1999. The events occurred 15 days after administration of the lipid complex The patient was rehospitalized on August 2 for recurrent abdominal ascites and pain; the patient was discharged on August 7 under pain management with suspicion of colorectal melanoma mass. The original diagnosis for the ascites was submitted to the OBA in early September 1999. The principal investigator believed that the ascites were "possibly related" to allovectin-7. The patient was removed from study on August 31 due to disease progression, with lesions i the lungs, mass in the colorectal area, and ascites; the patient died on September 17, 1999. The autopsy report

indicated the cause of death as multifactorial—metastatic melanoma, hyperprofusion due to heart failure, apoxia due to anemia and reduced pulmonary function, and several days' absence of fluid and nutrition. Lung/airway collapse and peritoneal ascites were attributed to the decrease in pulmonary function. No clear indication as to the cause of the ascites was provided.

"Possibly related" was not a category in the protocol; therefore, the investigator had to classify the event as "probably related" to the allovectin-7. Dr. Greenblatt received a letter, faxed from the OBA, in which the Institutional Biosafety Committee (IBC) at the University of South Florida, which had three allovectin-7 protocols undergoing, expressed its vote to suspend all ongoing human gene transfer trials involving the administration of allovectin-7. This institution was not the one at which the patient under discussion was treated. The study was suspended, despite the fact that more than 300 patients had been treated with allovectin-7 and ascites had never been reported and only a total of six unexpected serious adverse events (SAEs) were reported, none of which was attributed to allovectin-7. The IBC asked for additional information showing that patient safety is not compromised by administration of this agent and requested that the informed consent form be revised to state this information clearly.

Dr. Steve A. Kradjian, Vical (sponsor of the IND), stated that a previously planned safety review is taking place and that no safety issues have been found. The IBC asked for additional information but only after suspending the trial.

Dr. Greenblatt added that a concern was reported in the media that a vaccine used at St. Jude Children's Research Hospital, Memphis, TN, possibly was contaminated with HIV. On February 17, 2000, the FDA announced that HIV tests of the vaccine used in a gene therapy protocol at St. Jude contained no traces of HIV or hepatitis C virus (HCV) and that no patients on that neuroblastoma trial were ever exposed to contaminated vaccine. The National Cancer Institute (NCI) responded to a number of calls from patients on clinical studies at the NCI who were concerned that they had been infected with HIV; the NCI reassured them that all vaccines were tested for HIV and were found negative.

VIII. Other Issues

Dr. Noguchi provided an update regarding the March 6, 2000, letter sent by the FDA to all gene transfer IND sponsors regarding concerns about the manufacture and testing of gene transfer products, citing two main points:

- After years of gene transfer experiments, it is not always known which lot of vector is used in which patient. The first portion of the letter was a call to sponsors to routinely update the FDA with information on vectors, cell banks, and quality-control release specifications that deal directly with AEs by providing data on the history of products.

- The second part of the letter dealt with the monitoring of clinical trials. FDA regulations include a requirement for study sponsors to have in place a plan to monitor the clinical site and ensure that appropriate actions are being taken at the local level. Sponsors who already have INDs were required to submit, within 3 months, plans for monitoring ongoing clinical trials. The FDA will review these plans and provide feedback. New INDs also will be required to submit this information, ensuring appropriate infrastructure before a clinical trial begins. The FDA inspects institutions when a product is about to be licensed or if the FDA becomes aware of a deficiency.

Dr. Aguilar-Cordova and Dr. Mickelson both stated that the RAC must be careful, in its efforts to offer information to the public, to disclose appropriate (and not partial) information that is not out of context. Partial information may lead to more harm than good, which is what happened regarding the putative contamination of vector in the St. Jude trial that was reported recently in the media.

Dr. Gordon suggested that the RAC discuss, at a future meeting, the issue of when confidentiality is prudent and

when it is no longer necessary. Dr. Aguilar-Cordova stated that the RAC must be careful about what it requests and a what stage information is requested, since everything that comes to the RAC becomes public information. Asking fo all information at an early stage may lead to public disclosure of data that may not be interpretable by the public, suc as the results of an RT-PCR assay. Dr. Ando remarked that this topic will come up during the discussion of SAEs, at which time it is likely to be more controversial because immediate SAE reports are not confirmable.

IX. Day One Closing/Dr. Mickelson

Dr. Mickelson thanked all the participants and adjourned the first day of the March 2000 RAC meeting at 4:30 p.m. on March 8, 2000.

X. Day Two Opening Remarks/Dr. Mickelson

Dr. Mickelson opened the second day of the March 2000 RAC meeting at 8:00 a.m. on March 9, 2000. She reviewed the first day's discussions and previewed this second day's agenda.

XI. Discussion of Human Gene Transfer Protocol #0001-381: *Gene Therapy of Canavan's Disease Using AAV for Brain Gene Transfer*

Principal Investigators: Dr. Paola Leone, Thomas Jefferson University

Dr. Frederick A. Simeone, Thomas Jefferson University

RAC Reviewers: Drs. Aguilar-Cordova, Friedmann, and Macklin

Ad Hoc Consultants: Dr. Martha C. Bohn, Northwestern University Medical School

Dr. Nicholas Muzyczka, University of Florida

The principal investigators provided a 15-minute presentation of their protocol, the reviewers discussed their concern (with time allotted for responses), and the RAC and the public presented additional questions.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were eithe unresolved or novel and that the protocol warranted public discussion. These issues included: 1) the first protocol to propose using a viral vector to treat a degenerative genetic disorder by gene transfer into the brain; 2) concerns about adequacy of animal data regarding transgene expression of the AAV vector in the brain, its stability of *in vivo* expression and effect of substrate accumulation *in vivo*; and 3) an apparent overoptimism about the therapeutic effect, which could affect the parental consent for very sick children.

Drs. Aguilar-Cordova, Friedmann, and Macklin submitted written reviews, as did *ad hoc* reviewers Drs. Bohn and Muzyczka, to which the investigators responded in writing. Major concerns expressed in the written reviews include degree of risk to participants, safety monitoring, whether evaluations of efficacy were planned for this Phase I study, results of animal studies, nature and lack of completeness of preliminary data and scientific rationale, level or stabilit of aspartoacylase (ASPA) target cells, expression of the vector, a possibly unwarranted assumption of no AAV vector damage or toxicity, data on transduction of $1x10^6$ cells bringing about potential therapeutic effect, dose escalation, duration of level of expression required, product issues and how to compare vector across lots to ensure equivalence, risk-benefit analysis, use of nonhuman primates, proof that transgene expression affected neuronal function, whether

vector spreads to other tissues, and the issue of sufficient proof of principle.

Protocol Summary

Canavan's disease (CD) is a progressive degeneration of the brain, characterized by severe motor and mental retardation, which leads to death during childhood, usually within the first 10 years of life. There is currently no established treatment for CD. It is caused by a mutation in the ASPA gene, which results in a deficiency of ASPA enzyme in the brain. There is considerable evidence that the injury to the brain and the neurological impairments are caused by the accumulation of a chemical called N-acetylaspartate (NAA) in the brain, which is normally present in certain parts of normal brain but is ordinarily broken down and recycled by the enzyme ASPA. When levels of ASPA are too low, the NAA levels in the brain rise to dangerous levels. Through mechanisms that are still incompletely understood, the high levels of NAA eventually lead to cell death in the brain, especially in so-called glial cells that are involved in the formation and maintenance of myelin. This damage to myelin results in widespread impairment of nerve conduction in the brain.

The rationale of this study is that CD may be safely and effectively treated using a gene replacement procedure. Investigators plan to deliver the ASPA gene to cells of the brain using a nontoxic viral delivery system, recombinant adeno-associated virus (rAAV), to produce functional enzyme. In preliminary research trials in children in New Zealand and the United States, researchers demonstrated that both the ASPA gene and the previous delivery vehicle were well tolerated and were associated with some positive changes.

However, the previous formulation (an AAV-based plasmid/condensed lipid vector) was found to be less effective than the new one the investigators propose to use in this study. This Phase I trial aims primarily to test the safety of t procedure in humans; however, if sufficient delivery of the gene occurs, researchers hypothesize that the resulting increase in enzyme produced will lower the levels of NAA and help slow down progression of the disease. The study is divided into three phases: pretreatment, surgery, and postgene delivery. The pretreatment and posttreatment phases involve testing to assess the safety and potential benefits of the procedure. The risks of this procedure include those related to the surgical procedure and to the introduction of a synthetic gene using a viral delivery method.

RAC Discussion

Dr. Friedmann stated his belief that this proposal is not ready for implementation, although he averred that this diseas model is compelling because of its medical urgency and lack of other acceptable treatment. His review centered on h belief that the preliminary data and the scientific rationale are not complete enough to warrant moving forward. His specific concerns were (1) evidence of the levels or stability of ASPA expression in suitable target cells; (2) use of suitable animal models for toxicology and pharmacology studies and also to show proof of principle that delivery of this gene by this vector will result in gene expression but also evidence for phenotypic expression of the disease phenotype; (3) the assumption that expression from the viral vector will be more efficient than from the liposomal vector; (4) the statement that the overall level of transduction is more important than the transduction and efficient ge expression in a specific cell type; and (5) that a million ($1x10^6$) transduced target cells would be a sufficient number to bring about phenotypic and therapeutic effects in the human.

Dr. Aguilar-Cordova's review echoed Dr. Friedmann's concerns, while commending the researchers for their dedication to this tragic disease. Specifically, he was concerned about (1) dose escalation and the differences betwee the two groups (three vs. six bur holes in the cranium); (2) the possibility of using intrathecal delivery of the vector rather than through bur holes; (3) duration and level of expression required; (4) product issues, since the product will be made in New Zealand and no data were provided about how researchers would compare product among lots; (5) the reasoning behind choices such as dose, volume, number of bur holes, and intracranial stereotactic vs. intrathecal administration; and (6) comparison of the dose given in monkey studies (in which no toxicity was seen) vs. the proposed dose for humans.

Dr. Macklin's written review addressed ethical aspects, including recruitment of subjects, risks and benefits, informe consent, compensation in case of injury, and economic considerations. During her oral summary of the review, she focused on the risk-benefit analysis, including the level of risk (an admittedly value-laden judgment) and the fact tha the likely risks appear to be assessed differently by the RAC reviewers and the investigators. After taking into accou the RAC reviewers' queries and the investigators' responses, Dr. Macklin concluded that the risk-benefit ratio is unfavorable in this protocol. She reiterated that "the principle of hope," although a noble principle, has little to do wi the protection of human subjects and the responsibility of an IRB or the RAC to judge risk-benefit ratios.

Dr. Bohn, *ad hoc* reviewer, stated her concurrence with Dr. Friedmann's concerns. She advocated testing the vector on a large, nonhuman primate brain because of the involvement of the unique tissues of the nervous system. Dr. Boh asked that, at the least, the investigators conduct preclinical studies using the same injection parameters and vector to show widespread levels of expression and degree of stability of the transgene expression. Her additional concerns included details of the injection paradigm (flow rate and subcortical injection), host response to vector administration, whether redosing in the CNS of a primate is possible, possible effect on neuronal function, and possible vector spread to other tissues. Dr. Bohn reemphasized her belief that efficacy should be demonstrated in an animal model before clinical trials begin.

Dr. Muzyczka, *ad hoc* reviewer, summarized his review by raising the following issues: (1) whether there is sufficien proof of principle, that is, whether this vector system produces a reasonable amount of expression; (2) appropriatenes of the cellular target; (3) possible neuronal toxicity; (4) the use of cell culture neurons to evaluate the toxicity of ASPA overexpression; (5) concerns about the injection volume, which appears designed to cause an edema; (6) evaluation o vector stability; and (7) use of alternative animal models (e.g., injecting large amounts of NAA into normal rat brains and attempting to reduce NAA levels).

RAC Questions and Comments

Dr. Gordon noted the difficulty in evaluating this proposal because of the absence of information about how much expression per cell is needed to achieve a result and whether the desired effect must come from inside the cell. He als expressed concern about whether efficacy could be assessed and, if so, what methods would be used.

RAC members and the investigators generally agreed that insufficient preclinical data had been provided to the RAC with the investigators' original submission. Dr. Leone clarified that toxicology and gene stability data are currently being generated in rats and primates and will be provided to the RAC. Regarding proof of principle, she stated that th researchers have shown that they can transduce ASPA in the fibroblast and correct the phenotype of the fibroblast by increasing the level of ASPA, which breaks down NAA and is an average of fifteenfold higher. She offered to provide all the data collected concerning the different promoters and titers and the vectors with different purification methods; this data collection has been ongoing for 3 years. Dr. Leone indicated that, although investigators would lik to use intrathecal injection or intracerebral ventricular injection, they cannot; this avenue was proven ineffective in 4 years of data looking at T1 signal changes in different areas of the brain.

Regarding the problem of not having access to a transgenic mouse model, Dr. Leone stated that investigators have been discussing a collaboration with Dr. Reuben Matalon (University of Texas Medical Branch, Galverston, Texas) who developed the model for the past 6 months; however, Dr. Leone conceded that free access to this animal model might not be possible for an indefinite period due to complicated future funding problems. Investigators have ordered baby synonymalogous monkeys, on whom preclinical testing will be performed.

Regarding determination of the sufficient level of expression, Dr. Leone agreed that such information is currently unknown. Investigators intend to design and examine toxicology data in baby monkeys and rats to design the safest possible clinical protocol in patients. Transgene expression can be determined by noninvasive nuclear magnetic

resonance (NMR) spectroscopy to indirectly study drops of NAA.

Regarding spreading of the vector after intraparenchymal injection, Dr. Leone explained that spreading of the vector is based on the titer of the vector as well as on the flow rate used to deliver the vector. Researchers chose the optimal volume, the optimal titer, and a flow rate that is optimal for the risk-benefit ratio of patients undergoing a long surger

In the rat brain, Dr. Leone explained, researchers focused on the hippocampus and determined that by injecting up to 10 μL of non-small-cell ASPA at the rate of 4 microliters per minute, a 28-fold increase in ASPA is seen in the injected area in the hippocampus after 1 month. A fifteenfold increase in the contralateral hippocampus and a ninefold increase in the frontal cortex also were observed. These increases indicate a wide spread of the gene or, at the least, o the messenger RNA (mRNA).

Dr. Matthew During, Thomas Jefferson University, summarized additional research related to this protocol by stating that, by reinjecting AAV at 2-month intervals, transgene expression has been devoid of any systemic immune response.

Dr. Gordon requested clarification of the RAC's mission, which he believes does not include approval or disapproval of protocols but rather examination of potentially novel aspects of protocols that bear on safety, ethics, and science. Dr. Mickelson confirmed that the RAC does not have approval authority for protocols; the RAC makes recommendations to investigators and their institution's local oversight committees and to the FDA.

Ms. King opened discussion about research on children. According to DHHS regulations, such research is "not otherwise approvable" if it presents more than minimal risk and no prospect of direct benefit. Ms. King suggested tha the RAC recommend that, at this stage, this protocol does not present a reasonable opportunity to obtain the information that would outweigh the problem of not being able to argue that direct benefits are reasonably possible; this recommendation was not included in the list approved by the RAC as Committee Motion 3 (see below).

The following 11 suggestions/recommendations were offered by RAC members:

1. Submission of this protocol should be amended to include additional preclinical data on the level of gene transfer and expression in normal animals. These data exist but have not been submitted.

2. Detailed results from the first two CD trials (of nonviral systems) should be provided by the investigators.

3. Observable benefits, as described by parents, must be placed in the proper prospective, using objective and clear data on benefits seen in previous trials and any AEs encountered in those trials.

4. The investigators should further evaluate other possible routes of delivery.

5. The data collectible from this study should be expanded to be generalizable to future studies using AAV vectors in CNS applications.

6. A concerted effort should be made to determine the characteristics of improvement in CD, so that when any therapy is applied to this disease, the success of the strategy can be measured appropriately.

7. The data from planned studies on the monkey brain are essential to demonstrate efficacy and safety of injections into the brain at the volumes and flow rates suggested. Investigators should expand on the use of the newborn primate brain model.

8. Data are needed to support the conclusion that delivery of 30- to 50-fold volumes to the brain will not produce hemorrhage.

9. Clear presentation of the animal data in mice or nonhuman primates should provide a better understanding of the levels of transduction and expression. It is essential to track which level of transduction produced a specific level of enzyme and to ascertain whether that level is within the therapeutic range.

10. It would be helpful for the RAC to know on what grounds (under 45 CFR 46 Subpart D - *Additional Protection for Children Involved as Research Subjects*) IRB approval occurred for this protocol that proposes research with children. (This notation was made relevant to the current protocol and was extended as a general request to all other protocols involving clinical research on children.)

11. Information about the IRB's assessment of benefit affecting the risk-benefit ratio and the IRB's assessment of approvability would be helpful to the RAC, even if the data to support those assessments are not yet published. (This notation was made relevant to the current protocol and was extended to all other protocols.)

Public Comment/Dr. Roger Karlin and Dr. Helene Karlin

The parents of Lindsay Karlin, the first child treated for CD by gene transfer to the brain, described their child's problems. Researchers never promised special benefits but always emphasized safety. Lindsay's first gene transfer trial clearly improved several measures of her functioning. These effects persisted for 9 to 12 months, but Lindsay needed to be reinjected three times. Compared with the liposomal vector, the vector proposed in this protocol can reach most of the brain and thus provide a greater impact on the lives of affected children. Lindsay has improved and not deteriorated, whereas other children not treated with gene transfer show significant brain atrophy. There is no time to wait for an animal model; in any event, treatment in animals does not always reflect what happens in humans. Affected children have an ethical right to this treatment, as long as it is safe. The Karlins indicated to the RAC that, in their opinion and experience, not allowing this protocol to go forward would be a death sentence.

Committee Motion

In conclusion, the RAC found that the submission materials lack adequate supporting preclinical as well as clinical data from previous studies to proceed with this protocol. The committee requested written response from the investigators outlining their response to the recommendations listed below:

Provide the RAC with a summary of the available clinical results and adverse events, if any, of the ongoing Protocols #9708-211 and #9711-222. A manuscript accepted for publication would be a sufficient source of the information.

Provide the RAC with the safety and toxicity data from nonhuman primate models including the extent of infection, levels of gene expression over time, neuropathological assessment of injection sites, demonstration of lack of spread of vector to other tissues, and demonstration of lack of functional effects of the transgene in normal animals. The desired data are those comparing different routes of AAV delivery to the brain using the actual vector construct and injection paradigm to be used for the patients and data from the newborn primate. Data from other laboratories are acceptable provided that the investigators can gain access to and be allowed to review and submit the data in support of the protocol.

The RAC noted the regulation in 45 CFR 46 - *Protection of Human Subjects* and 45 CFR 46 (Subpart D) - *Additional Protection for Children Involved as Research Subjects*, that the level of risk to children

must be assessed. In this regard, the RAC requests that the investigators provide the information regarding their Institutional Review Board's deliberation of the protocol's risk level.

A motion was made by Dr. McIvor and seconded by Dr. Aguilar-Cordova to include the above recommendations in a letter to the investigators. The motion passed by a vote of 13 in favor, 0 opposed, and 1 abstention.

XII. RAC Working Group on Current Issues in Adverse Event Reporting

Working Group: Dr. Macklin (Chair); Drs. Ando, Friedmann, Juengst, Markert, and Mickelson; Ms. King and Ms. Levi-Pearl

Ad Hoc Consultant: Dr. Gary B. Ellis, OPRR

Definitions, Data, and Current Issues/Dr. Patterson

Dr. Patterson reviewed several basic definitions. According to the Code of Federal Regulations, a serious adverse event (SAE) is any adverse drug experience that occurs at any dose that results in one of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event, when, based upon appropriate medical judgement, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. SAEs are classified by their consequences; seriousness is not synonymous with severity. An AE is reported in three basic elements: seriousness (consequence and severity), association with gene transfer (possibly, probably, or definitely), and expectedness on the basis of prior experience with the investigational product.

Dr. Patterson provided a table summarizing the NIH and the FDA reporting requirements, the former of which are currently under review. A timeline of events and issues that have developed subsequent to Jesse Gelsinger's death was also presented. The adenoviral safety and toxicity (AdSAT) data contained reports of 970 SAEs, whether or not they were associated with the intervention. In 1999 the OBA received 103 spontaneous, investigator-initiated submissions; 464 unsolicited reports have been received so far in 2000, with no attribution as to cause. Of the 970 SAEs received in response to the AdSAT request, 85 (9 percent) are serious, unexpected, and possibly associated; 0.1 percent (one person) is serious, unexpected, and definitely associated (Jesse Gelsinger). For the period January through March 2000, 9 percent of the SAE were initially reported by investigators as serious, unexpected, and possibly associated.

Current issues in AE reporting include noncompliance with reporting requirements and labeling SAEs as proprietary, both of which preclude RAC review and public awareness. The *NIH Guidelines* currently lack a definition of AEs and an explicit timeline for reporting AEs. These issues are under active consideration by the RAC as well as by a Working Group of the Advisory Committee to the NIH Director.

Definitions, Attribution, Grading, and Reporting Requirements/Dr. Greenblatt

Dr. Greenblatt explained that an AE is any untoward medical occurrence, in a patient or clinical investigation subject who is administered a pharmaceutical product, that does not necessarily have a causal relationship with the individual's treatment. Thus, an AE can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal or an IND, whether or not it is related to that product. An AE is considered associated with the use of the product if there is a reasonable possibility that the experience may have been caused by it.

Attribution is the determination of whether an AE is related to a medical treatment or procedure. As used by the NCI the five categories of attribution are definite, probable, possible, unlikely, and unrelated. The severity of an AE is graded from 0 to 5, the scale used by the NCI, that is, from no AE or an event that falls within normal limits (rated 0) to a fatal AE (rated 5). This scale allows for uniformity in grading AEs. The NCI is currently piloting the Adverse Event Expedited Reporting System (ADEERS), an electronic, Web-based reporting system for the expedited reporting of SAEs seen in NCI-sponsored clinical trials. The system will be used to capture electronically all SAEs and unexpected AEs.

Often it is not possible to classify an AE as related to or expected in connection with a study agent until several simil AEs have occurred. The symptoms of the AE may overlap with the toxicity of the investigational agent; for example, elevated liver enzymes could be caused by the investigational agent or by a tumor that has metastasized to the liver. Knowledge of the toxicity seen in preclinical animal studies can be helpful in deciding whether a specific AE is related to the use of a specific study agent.

Dr. Greenblatt discussed two examples—motor neuropathy and dyspnea—from a protocol involving the use of Ad-p53 in patients with non-small-cell lung cancer to illustrate what happens when an AE is reported to the NCI. For this protocol (#9406-079), 38 of the 48 patients died; most of these deaths were attributed to progressive disease, and there was no evidence of decreased median survival. Three of the thirty-eight deaths were considered possibly related to the treatment, but after closer examination of the data, it was concluded that no deaths were related to the treatmen

Draft Report of the Working Group on Current Issues in Adverse Event Reporting and Discussion/Dr. Macklin

Dr. Macklin stressed that the Working Group was presenting a draft report that does not include consultation with the FDA and represents the thinking of only a subset of the group. All previous comments during public meetings were taken into account.

The Working Group is charged with making recommendations on the reporting of SAEs. The Working Group could not reach a general consensus, although the members did agree that it is desirable to harmonize NIH reporting requirements with those of the FDA, as much as possible. However, several factors hinder complete harmonization of reporting requirements:

- The difference in the timing of reports. Sponsors report to the FDA, and investigators report directly to the OBA rather than through the sponsors.

- Uncertainty in determining whether an SAE is "possibly related" to the gene transfer procedure, a requirement only apply to FDA reporting.

- The difficulty that may arise in determining whether an SAE is "expected," given the novelty of some of the protocols in the earliest phase of GTR, including the first use of the procedure in humans.

- The general reporting requirements of the FDA, which are applicable to all research that the FDA oversees, in contrast with OBA reporting requirements, which apply to a smaller subset of research that contains many novel features.

For these reasons, complete harmonization is difficult to achieve without compromising the protection of human GTR subjects.

The majority of the Working Group members who responded (six responded and five concurred) agreed on the

following points:

1. Definition of "adverse event" is as Dr. Greenblatt presented it, and thus the Working Group recommended that it be harmonized with the FDA definition.

2. Definition of "serious adverse event" is harmonized with the FDA definition in 21 CFR 312.32..

3. Definition of "associated with the use of the gene transfer product" is harmonized with the FDA definition in 21 CFR 312.32..

4. Definition of "unexpected adverse event" is harmonized with the FDA regulations in 21 CFR 312.23(a)(3) and 21 CFR 312.32..

Points 5, 6, and 7 proved more problematic and resulted in significant discussion among RAC members, as follows:

5. Principal investigators who have received authorization from the FDA to initiate a human gene transfer protocol must report immediately in writing (1) all serious AEs possibly associated with the use of the gene transfer product, whether expected or unexpected, and (2) all unexpected AEs possibly associated with the use of the gene transfer product, whether serious or not. Immediate written reporting requires submission as soon as possible but no later than 15 calendar days after such an event has occurred. In addition, investigators shall report to the OBA by telephone or facsimile any unexpected fatal or life-threatening experience as soon as possible but no later than 7 calendar days after the investigator's initial receipt of the information. Reports to the local IRB, IBC, and the OPRR (if applicable) should follow FDA reporting requirements.

Comments and questions about this section included the following:

• Why ask investigators to report expected AEs immediately? Such events would be picked up in annual reports, would appear in the consent forms, and should not need to be verified in real time. Reporting all unexpected AEs that are possibly associated raises the issue of whether an event is possibly associated or not. Very sick patients experience many such events, and it would be difficult (and a great burden to investigators) to state that an AE was definitely not related.

• Point 5 says the principal investigator should submit the reports; FDA regulations state that the sponsor should submit them. This reporting should be uniform.

• The term "immediately" should be redefined as "more than once a year."

• Followup reporting about SAEs would be helpful.

• Unexpected events (even if not serious) are useful because they could be warnings about SAEs to come.

• The amount of information the RAC would be required to see "immediately" could be voluminous. If an AE is reported immediately and the RAC does not act immediately, culpability may be an issue.

• Signal-to-noise ratio should be considered. It is important that the RAC not allow the

important reports to get lost in the larger numbers of immediately reported AEs.

• How does immediate reporting benefit the RAC and the public? The RAC is not a regulatory body but is constituted to look at trends.

• Consideration should be given to removing the requirement of immediate reporting to the NIH; instead, "digestible" information should be reported to the RAC for public consumption. Someone needs to distill the AE information; raw data are not helpful.

• A standardized form for reporting AEs to the NIH should be created. Then those reports should be distilled, and the RAC should be informed relatively quickly.

6. A procedural mechanism should be established at the institutional level to ensure the accuracy and reliability of judgments that an AE is "possibly associated" with the gene transfer. This mechanism could consist of review and documentation by an individual who is not a member of the research team or by individuals who normally review AEs that are submitted to the IRB.

Comments and questions about this section included the following:

• Bad diseases produce numerous AEs (not necessarily serious ones). It would be impossible for IRBs to review all AEs, which would involve thoughtful review of medical records, a process that is not possible with the current setup of IRBs.

• Most people who classify AEs would categorize almost everything as "possibly" related.

7. A national DSMB should be established for GTR. The DSMB should have a broadly representative membership and considerable expertise.

Comments and questions about this section included the following:

• The goals and reasons for establishing a national DSMB should be clearly set forth. This seems to be a reaction to the University of Pennsylvania death in the ornithine transcarbamylase (OTC) trial, but having a DSMB in place would not have affected the outcome. This problem should be addressed using audits—detailed documentation on production and good clinical practice.

• Instead of a DSMB, set up an exact parallel reporting mechanism and timing (NIH and FDA) but remove patient identifiers because of the RAC's public discussions.

• Serving on a DSMB would be a full-time job. DSMBs are usually set up for Phase III studies and are not the best way to look at Phase I and II studies.

• DSMBs cannot respond in real time since they only meet periodically and receive data in clusters.

General comments from RAC members included the following:

• The RAC is responsible for novel concerns. Some of the "expected" AEs may need to be defined more precisely.

• The FDA has the experience and expertise to evaluate AE reporting. To ask the NIH to do this would be a mistake.

• Jesse Gelsinger's death may not indicate a problem with the current reporting system. Gene transfer is different from classical drug treatment trials, and there is less experience with it. A new mechanism may not be necessary to help allay concerns.

• Receiving the wrong data could be dangerous: Data can be easily misinterpreted, especially by nonexperts, and the presence of data is not equivalent to having usable information. The RAC does not have the expertise or personnel to evaluate AE reports.

• The FDA is not yet in the position to disclose AEs *ad hoc*; however, a rule is currently undergoing FDA clearance to report AEs publicly, possibly via the RAC.

• The letter sent by Dr. Jay P. Siegel, FDA, on March 6, 2000, to all investigators involved in gene transfer research covers concerns on quality assurance and clinical practice.

Dr. Macklin summarized the situation as a stalemate: The majority of the Working Group members concurred with t report as written, but the rest of the RAC membership did not. One reason for immediate reporting to the RAC is to get the word out to patients in other trials; the result of this notification may cause re-consenting the patients or at least notifying participants. (For example, an AE may be occurring significantly more frequently, even if it is an expected event.) The FDA is not publicly mandated, so if the RAC believes information should be made public, another AE reporting mechanism is needed to communicate with investigators and with IRBs. A current requirement mandates the reporting of all AEs to IRBs, so harmonization could be with IRBs rather than with the FDA.

Dr. Mickelson stated that the Working Group was formed in response to the December 1999 RAC meeting, the OTC trial at the University of Pennsylvania, and other issues raised by the public. The Working Group will continue its deliberations, and its membership was increased by the addition of Drs. Breakefield, Gordon, and Greenblatt. Dr. Mickelson noted the critical importance of engaging other individuals and groups with interest in this area and hearin public comments on the issues being considered by this Working Group. The objectives of patient protection, nonconfidentiality, protection of the public, and access for patients are absolutes, and the reporting burden on investigators will also be taken into account.

XIII. Discussion of Human Gene Transfer Protocol #0001-371: *A Phase I Safety Study in Patients With Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector To Deliver the Gene for Human Factor IX Into the Liver*

Principal Investigators: Dr. Bertil Glader, Stanford University

Dr. Mark A. Kay, Stanford University

RAC Reviewers: Drs. Breakefield, Juengst, and Wolff

Ad Hoc Consultants: Dr. Mark W. Kieran, Dana-Farber Cancer Institute and Children's Hospital, Boston

Dr. Nicholas Muzyczka, University of Florida

The principal investigators provided a 15-minute presentation of their protocol, the reviewers discussed their concern (with time allotted for responses), and the RAC and the public presented additional questions.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were eithe unresolved or novel and that the protocol warranted public discussion. These issues included: 1) a concern about injection into a liver vessel with a newAAV vector, and a need of animal toxicology data to assess such risk for the human subjects; 2) a concern about generation of inhibitory antibody to factor IX; and 3) questions of how the proposed trial differed from the ongoing trial of intramuscular injection of the same vector.

Drs. Breakefield, Juengst, and Wolff submitted written reviews, to which the investigators responded in writing. Major concerns expressed in the written reviews included the safety of the intrahepatic artery (IHA) injection procedure in patients with severe hemophilia, the need to see results of animal toxicology studies to assess the risk fo human subjects, data on vector distribution via the IHA route and ectopic sites of infection, measures for assessing toxicity and at what toxicity level dose escalation would be halted, why the investigators want to move on to Factor IX (hFIX) intrahepatic gene delivery to the liver while a trial for intramuscular (IM) delivery is ongoing, histopathological data on dog and rat studies, readministration of AAV engineered for expression of human clotting Factor IX (AAV-hFIX) vectors, assessment of the relative infectibility and toxicity of the AAV virion to human hepatocytes in culture, and the financial involvements of Drs. Kay and Glader with Avigen (the company making the vector for this trial).

Protocol Summary

Hemophilia B is the bleeding diathesis that results from a deficiency of blood coagulation Factor IX. The disease is X-linked and affects approximately 1 in 30,000 males. Most individuals with hemophilia B have severe disease, with Factor IX levels of less than 1 percent of normal. The major morbidity is arthropathy from recurrent spontaneous joint bleeds; the major mortality factor is CNS hemorrhage. The prevalence of CNS bleeding ranges from 2.6 to 13.8 percent, with mortality rates between 20 and 50 percent and morbidity rates (seizures, motor impairment, or mental retardation) between 40 and 50 percent in survivors. These bleeds occur predominantly in patients with severe diseas (less than 1 percent factor level), thus supporting the concept that raising the levels of factor even slightly would improve the chances of avoiding this life-threatening complication of the disease. The incidence of arthropathy and of CNS hemorrhage can be reduced by the use of prophylactic regimens, whose goal is to maintain trough factor levels greater than 1 percent of normal. Since there is direct correlation of the severity of the disease with the level of Facto IX, analyses of hemostatic parameters (particularly whole-blood clotting time and activated partial thromboplastin time) and hFIX provide readily quantifiable measurements of treatment efficacy.

Recombinant AAV vectors have been shown to result in safe and efficacious gene transfer when administered into th liver of animals that suffer from hemophilia B. The overall purpose of this research is to determine the safety of IHA injection of an AAV vector expressing hFIX into patients with severe hemophilia B. Investigators will evaluate the safety of interpatient dose escalations of AAV-hFIX administered into the hepatic artery. Toxicity related to the delivery of AAV-hFIX will be evaluated locally and systemically. This study will also determine whether inhibitory antibodies against Factor IX develop in patients receiving AAV-hFIX by IHA administration, whether gene transfer is affected by the presence of preexisting antibodies against AAV, the duration of expression of an AAV vector delivered to the liver in humans, and whether therapy with AAV vector results in transfer to human germ-line cells. The potential efficacy will also be evaluated by measuring the presence and activity of the transgene product. Analyses will be done to detect the presence of protein expression in blood by measurement of hemostatic parameters and Factor IX antigen by ELISA.

RAC Discussion

Dr. Breakefield began her review by noting that use of the AAV vector is relatively new in human clinical trials, so

few data are available. This disease is not life threatening (although it is life compromising) and is treatable to some extent; as a result, the concern about relative risk-benefit must be addressed. Her other concerns included the lack of data on nonhuman primates, the use of the IHA injection route, relative infectivity of AAV vectors in primates (including humans) compared to rodents and dogs, the possibility of negating current standard therapy by stimulating inhibitor formation, and the possibility of genotyping prior to the procedure to determine which patients have missense mutations.

Dr. Wolff apologized for the lateness of his written comments to the investigators. He prefaced his review by stating that these investigators have done "a great job" of setting the standards for clinical gene transfer trials. His concerns about this protocol include the question of inhibitor antibodies, whether it would be worthwhile to look at the Alabama dog model for neutralizing antibodies, injection of nonhuman primates with this vector before proceeding t humans, AAV interaction with endogenous viruses such as HIV or hepatitis viruses, and whether a human hepatitis model in animals can be used to examine the safety issues. Dr. Wolff also wondered whether the investigators shoul await the results of the higher doses of the IM injection studies before proceeding with this trial, again looking for neutralizing antibodies.

Dr. Juengst echoed the comments of Drs. Breakefield and Wolff and specifically discussed the possibility of the researchers waiting for the results of the IM studies. He stated that the consent form is a model, that stresses the potentially nonbeneficial and experimental nature of the protocol, which is particularly important for this cohort because maintenance therapy can be obtained outside of the study.

Dr. Kieran, ad hoc reviewer, reiterated the comments already offered by the RAC reviewers. He brought forth a general issue about how much primate testing is required to feel safe, particularly in using new routes of administration. His other concerns included direct IHA administration and possible toxicities in a patient population with underlying hepatic disease and a bleeding disorder, the potential development of inhibitors, the meaning of directly applying virus to an organ that may not be functional and whether animal data speak to this issue, and wheth this trial would be appropriate if the results of the IM trial indicate expression of Factor IX.

Dr. Muzyczka, ad hoc reviewer, concurred with the comments already presented. He also wanted the investigators to comment on how they would deal with the inhibitor problem if it arises. He queried whether liver primate experimen with AAV have been conducted, even though IM and aerosolization to the lung in primate experiments have been uneventful. Dr. Muzyczka asked the investigators to comment on any known *in vivo* or helper interactions of AAV with the hepatitis B virus or hepatitis C virus (HCV).

RAC Questions and Comments and Investigator Responses

RAC members concurred with the investigators that if these same investigators were not conducting the IM studies, they probably would not be asked to wait to begin this protocol until the IM studies were finished.

Dr. Kay explained that all the patients enrolled in the IM trial and patients who may be enrolled in other similar trials in the future are genotyped beforehand to select for missense mutations because of the greatly decreased risk of inhibitor formation.

In the clinical arena, Dr. Kay indicated that there are no data about the interaction of AAV with HCV; no animal models or cell culture models of HCV exist. The two viruses have been shown to work by different pathways. Because of the interaction of AAV in liver disease, patients with severe liver disease will be excluded from this trial.

Regarding the issue of inhibitor formation, Dr. Kay reiterated that, as was done in the IM trial, patients with missense mutations will be selected because, historically, these patients have not been prone to inhibitor formation. Although antigen presentation is different in patients with missense mutations, there are differences in antigen presentation when

using adenovirus vs. AAV.

Dr. Gordon asked about the long-term consequences of integration, to which Dr. Kay responded that the literature indicates no long-term consequences for AAV. The investigators have followed several dogs for more than 2 years, and there has been no evidence of AAV integration.

Dr. Kathy High, Children's Hospital, Philadelphia, addressed some of the reviewers' questions about inhibitor formation in gene-based treatment for hemophilia because she believed it to be the major safety issue. She reminded the RAC that, currently, the major complication of protein-based therapy for hemophilia is also the formation of inhibitory antibodies. Considerations about immune response to the transgene product and possible formation of inhibitory antibodies apply not just to hemophilia but also to all genetic null mutations. Dr. High reviewed several relevant animal studies to support her belief that—for every vector, transgene, and target tissue—detailed immunology studies must be conducted to examine the immune response of the transgene product; such studies are under way to support the currently proposed protocol. Dr. Kay informed the RAC that a product called recombinant Factor VII-A is now available. It is a protein that works in the coagulation cascade beyond where Factor IX works. Therefore, in the rare event of an inhibitor, the investigators now have a therapy available that has been used successfully in many children in the United States and Europe.

Ms. King asked about the monitoring responsibilities of the conflict of interest committee and the data oversight committee. Dr. Kay explained that the conflict of interest committee at Stanford University meets with the investigators periodically to find out which data have been generated, any AEs that have emerged, and who is doing what; for example, they ensure that Dr. Kay is not treating patients, because he is not a hematologist. The data oversight committee then reviews the data from time to time and ensures that proper analysis and safety issues are being addressed.

In response to the concern about beginning this trial before the IM trial results are available, Dr. Kay emphasized that a cure for hemophilia is not currently available and is not predicted to come from Phase I of the IM trial. Even if a therapeutic level that appears to benefit patients is achieved, several unknowns will still exist, for example, the frequency of inhibitor formation and the frequency of retreating. Because such information is not known, the investigators believe that multiple approaches to treatment are scientifically reasonable.

Dr. Gordon requested clarification on the idea of using gene transfer for a somewhat treatable disease. He stated his understanding that the standard therapy has many deficiencies in terms of burden to patients and an inconsistent level of Factor IX in the bloodstream of patients receiving the standard therapy; these problems present a satisfactory reason for going forward with this protocol. Dr. Glader concurred, stating that episodic treatment can control bleeding, but bleeds still occur. Prophylaxis would be helpful but is an impractical solution for most people because patients must be infused at least three times a week and the cost is $200,000 to $300,000 per year.

Dr. Noguchi discussed primate testing using AAV vectors. One of the differences between AAV and other vectors that toxicity is not exactly known. AAV has been administered intramuscularly and in the lung through aerosols in primates, as well as to dogs and mice. In these animal models, no SAEs have occurred, researchers have reported significant transduction, and the doses have reached therapeutic levels. It is not known what is the best animal model for assessing toxicity, but the hemophilic dog is posited as having the advantage of assessing efficacy as well as representing the genetic lesion that might compromise a human patient when it interacts with a vector.

Dr. Muzyczka asked the investigators to explain what they would do if inhibitory antibodies against Factor I develop, what the costs would be, and who would bear those costs. Dr. Glader responded that, if an inhibito developed, they would simply observe the patient for a while, because many inhibitors are transient and disappear. In the worst-case scenario, if the inhibitor is not transient, researchers will treat the patient episodically for bleeds using recombinant Factor VII-A, which is available and considered efficacious. The average cost for an average severe

hemophiliac is more than $100,000 per year for episodic treatment.

Public Comment

None.

Committee Motion 1

A motion was made by Dr. Breakefield and seconded by Dr. Markert to recommend that the investigators wa study involving the IM delivery of AAV vector to finish before initiating this liver study. The motion failed by a of 2 in favor, 8 opposed, and 5 abstentions.

Committee Motion 2

A motion was made by Dr. Breakefield and seconded by Dr. Markert that the investigators wait for the result ongoing nonhuman primate safety study of intravascular administration of AAV vector to the liver. The committ that delay until the safety data is available would be a prudent measure given the new kind of vector, vector dose, prior experience with adenoviral vectors using this route of administration in human trials, and that a nonhuman primate trial was near completion. The motion passed by a vote of 7 in favor, 3 opposed, and 4 abstentions.

During the comment period for this motion, Dr. McIvor stated that he did not feel comfortable with requiring these investigators to look at nonhuman primate studies when the FDA has already ascertained that the dog model is adequate; Dr. Breakefield reminded the RAC that this motion represents a recommendation, not a requiremen

XIV. Advisory Committee to the Director, NIH , Working Group on NIH Oversight Clinical Gene Transfer Research

Dr. Mickelson noted that members of this Working Group were present for this portion of the RAC meeting, and she read the group's charge: "As part of the NI's response to recent events, the NIH Director established a worki group of the Advisory Committee to the Director, NIH , to review the role of the NIH in the oversight of clini transfer research. The Working Group is encouraged to consult with other experts and solicit public comment in the course of its work. The Working Group is asked to develop recommendations to address the following questions:

- Is the current NIH framework for oversight and public discussion of clinical GTR appropria especially with regard to the respective roles of the RAC and the *NIH Guidelin*
- Are current NIH mechanisms adequate for coordination of the oversight of clinical GTR with the F OPRR , IRBs , and
- Are additional NIH measures needed to minimize risk associated with clinical G
- What should the NIH role be with regard to reporting, analysis, and public discussion of serious advers events?

Dr. Christine Cassel , Mount Sinai School of Medicine, discussed the logistics of the Working Group on N Oversight of Clinical Gene Transfer Research, which was formed as a broad group representative of different perspectives, with no vested interest in organizations or specific research under consideration. The Working Group was created by the NIH Director in early December 1999 and was charged to report in June 2000; however, Dr. I Kirschstein , Acting NIH Director, has requested recommendations and general conclusions by the end of Ap

The following questions, concerns, and recommendations were discussed:

1. The effect of changing the RA's responsibilities from approval to review of protocols. The RAC was divided on this issue, with a majority believing that the current public discussion/review coupled with recommendations (as opposed to approval responsibilities) works well. Comments included the following:

• The RAC has a great deal of influence by virtue of its public discussion. Investigators take the RAC seriously now; RAC comments become changes in protocol. Public discussions of novel protocols are more helpful to the field than RAC approval of all protocols.

• The RAC has contributed much more toward public understanding of GTR as a educational body than it could have done (or did in the past few years) with regulatory power. The RAC is stronger now and has a lot of influence, as powerful an influence as approval.

• When RAC members have serious concerns about a protocol, all they can do (in addition to communicating informally with the FDA) is use moral suasion. There are many pressures to proceed with these trials, so the "teeth" (approval responsibility) that were removed from the RAC should be reinstated.

• The RAC is currently a "debating society," with no direct concrete responsibility for consequences; other forums are available for this avenue. If the RAC is going to do the work of reviewing protocols, there should be some consequences, although direct approval is not necessary. Without consequences, the public is likely to develop a false impression of a quasi-governmental body with responsibilities.

• The RAC contains more expertise than that of any IRB . Accountability should b increased, but approval is not necessary. Oversight should be improved.

2. Timing of Reviews

• The timing of the structure of RAC review should be addressed—where RAC input should be inserted and the exact nature of that input. Unfortunately, the RAC deals with many issues that should have been resolved at the IRB level (e.g., issues related to Informe Consent forms).

• RAC review of protocols should occur at the pre- IND stage or before local IRB approv Currently, the RAC reviews studies already under way that appear before the RAC with policy, scientific, and/or consent problems. Expansion of the RAs infrastructure would be needed to handle the anticipated increased work of earlier review.

• Protocols were held up for many months while waiting for the IRBs and IBCs to final their reviews and approval and submit the protocols to the FDA and the RAC at the same time. Dr. Markert recommended that protocols be allowed to come to the RAC without ful IRB /IBC approval, still necessitating submission to those bodies but not necessarily requirin preapproval by the

3. Other issues:

• Followup . Discussion ensued about the 's responsibilities in following up on its recommendations to investigators. The RAC needs to have public closure on policy issues brought up by the novel protocols it reviews; one easy way to implement this closure would be to give the RAC some type of approval responsibility. Response authority could be set up so that investigators would not have to agree with the RAC but would have to respond in some manner.

• General process. Requesting RAC e-mail reaction to protocols is frustrating because RAC members are given little information by which to evaluate a protocol. Much confusion comes from having to act on insufficient information. This preliminary review process needs improvement.

• AE reporting:

– A consequence of the NIH Direct action in 1997 to remove approval authority from the RAC is the confusion about AE reporting. Investigators believed they were reporting adequately to other agencies to whom they had reporting responsibilities, so they did not report back to the RAC. Reporting requirements should be homogenized.

– The FDA is helped by discussion at RAC meetings, and the RAC should not take over AE reporting. A "filtration" subcommittee relating to AEs should be formed to bring AE reports to the RA's attention

• The RAC does not have a relationship with IRBs , but the RAC is an untapped advisor resource for them. Stronger oversight with IRBs would be helpfu

• The RAC is helping the FDA do its job. The relationship between the FDA and the RAC should be strengthened, but the two bodies should not duplicate effort with regard to protocols.

• Protection of the public should not get lost in any changes in the RAC process. The public needs to be confident that the mechanism in place is adequate.

Dr. Thomas H. Murray, president of the Hastings Center and a member of the NIH Working Group, summed up RA's assets and limitations as follows

• RAC assets: The RAC has expertise and experience (scientific and ethical); credibility; a high degree of objectivity; political and scientific independence; potential for a synoptic view of the science, risks, and clinical relevance; and the benefit of public deliberation.

• RAC limitations: The RAC has members who have "day jobs" (serving on the RAC is a voluntary position), a small staff, relative lack of statutory authority, unclear jurisdiction over non- NIH funde research, and lack of closure.

Dr. Markert responded to the Working Gr's query about whether additional NIH measures are needed to mini risks associated with clinical GTR by summarizing the March 6, 2000, letter from Jay P. Siegel, FDA, to al investigators who conduct GTR . She expressed belief that implementing the requests contained in that letter wil minimize the risks perceived to be present in the University of Pennsylvania OTC trial. The letter requires submissio

(in triplicate within 3-month lists) of all gene transfer products, a summary of all the lot release data, a summary of product-manufacturing quality assurance and quality control, the names of those responsible for overseeing this process, and the records. The investigators then must show that there is adequate monitoring of clinical investigation including compliance with good clinical practices and the names of those responsible for that monitoring; investigato must also provide an organizational chart indicating those responsible for all the different aspects of this regulation. This type of auditing (and proof that it has been completed) will greatly enhance the safety of clinical protocols, and Dr. Markert asserted that the FDA is the appropriate place for this auditing to occu

Dr. Aguilar-Cordova expanded on Dr. Noguchi's statement—that the RA's main function is to help the FD—by adding that the RAC is a sounding board for the public. The RAC can perhaps increase public confidence in GTR opening to public scrutiny the work of scientists and the kinds of clinical trials that are taking place.

Dr. David Parkinson, Novartis , commented that the FDA clearly stated its limitations in this review process. The field clearly needs something that the FDA cannot offer—public discussion. The digestion of clinical experience across biology, agents, and indications has not been done because of statutory problems related to the FDA dealing with and disseminating this information. The RAC is the voice of both the FDA and NIH . This role is compleme and not duplicative of FDA roles. In other therapeutic areas, the FDA must use other ways of releasing information t the public; however, in the GTR field, the FDA and the NIH use the RAC to perform this important funct

Dr. McIvor stated that, under the approval system, the status of a protocol was conveyed to the RAC as that protocol moved into the clinic. He explained that the RAC does not desire a return to approval authority; however, the RAC does want to receive information about protocol status. He concurred with Dr. Ando's suggestion that the RAC should revisit periodically selected protocols to determine accumulated safety and efficacy data.

Ms. Levi-Pearl reminded the RAC that patients who look to GTR as a hope for the future are concerned that thi enterprise will be stopped, either directly through mandate or indirectly by legislative oversight that will effectively hamper progress. The RAC needs to bear in mind that it carries a mantle that is larger than the RAC's actual charge. The RAC needs to regain the trust of and educate the public that this Committee, as an arm of the NIH , is doin everything that it can in terms of its rules, regulations, and understanding of the RAC mission to ensure that this research will proceed.

XV. Discussion of Human Gene Transfer Protocol #9912-363: ***A Phase I Study of the Replication-Competent, E1B– Attenuated Adenovirus With a CD/HSV-1 TK Fusion Gene and th Oral Administration of Valaciclovir in Adults With Penile Canc***

Principal Investigators: Dr. Brian J. Miles, Baylor College of Medicine

Dr. Gustavo Ayala, Baylor College of Medicine

Dr. Estuardo Aguilar-Cordova, Baylor College of Medici

RAC Reviewers: Drs. Chow and Gordon and Ms. King

Ad Hoc Consultant: Dr. Kamel Khalili , Temple University (written rev

Since the other two principal investigators were not able to attend this RAC meeting, Dr. Aguilar-Cordova provided short presentation of the protocol. The reviewers discussed their concerns (with time allotted for responses), and the RAC and the public presented additional questions.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were eithe unresolved or novel and that the protocol warranted public discussion. These issues included: 1) a concern about one week delay in pro-drug administration allowing the virus to spread to multiple organs after its replication in the targeted cancer cells, thereby increasing toxicity in nontarget tissues; 2) a concern of driving nondividing (cells into the S phase of the cell cycle by an adenovirus retaining its E1A gene; and 3) safety issues and questions about the risk-benefit calculus of the proposed protocol.

Drs. Chow and Gordon and Ms. King submitted written reviews, to which the investigators responded in writing. Major concerns expressed in the written reviews included typing of tumors for p53 prior to initiation of treatment; replication competence of the vector; normal cells being rendered vulnerable to valaciclovir toxicity; proximity o injection site to reproductive tissues; delay in standard therapy necessitated by this protocol; course of therapy planne if the treatment appears highly effective; biodistribution of the replication-competent virus; toxicity of this vecto seminal vesicles, gallbladder, testes, and liver; and consent form issues such as explaining the dose-escalation design avoidance of terminology suggesting possible efficacy, provision of more risk information, inclusion of a request for autopsy, and inclusion of a statement about media interest in the research.

Protocol Summary

Cancer of the penis is rare among males in the United States, accounting for 0.4 to 0.6 percent of all malignancies among U.S. men. Penile carcinoma is common, however, among men in some African and South American countrie and is one of the leading cancers among men in Paraguay. With no therapy, penile cancer is a relentless, progressive disease, causing death for most patients within just 2 years.

The most common treatment for cancer of the penis is surgical removal of a portion or all of the penis. Whether a patient requires a partial or total penectomy depends on the size, depth, and extent of the tumor, as well as the bo habitus (body mass index, body composition, or body fat pattern) of the patient. Current therapy, therefore, may in severe cosmetic deformity as well as significant modifications in voiding and sexual function. Alternative therapie such as radiotherapy have significant complications. New preoperative or perioperative adjuvant therapies are ne to reduce or eliminate the need for surgical management. Consequently, the investigators believe the risk associated with this new gene transfer approach in these patients is offset by the potential significant therapeutic benefit of reducing or possibly eliminating the cancer.

Direct introduction of therapeutic genes into tumor cells may provide an effective treatment for cancer of the penis. I this trial, investigators plan to use two strategies of gene transfer to treat penile cancer. First, the vector to be used in this trial is replication competent. This adenoviral vector, called Ad5-CD/*rep*, has been constructed so that its infection and replication preferentially affect tumor cells. The vector does this by recognizing that many malignant cells lack the functional signal p53 compared with normal cells. The second strategy is to confer drug sensitivity to tumor cells by inserting a recombinant gene into them. This gene is the common herpes simplex virus thymidine kinase enzyme (HSV-tk), which converts the antiviral drug valaciclovir into a form that is toxic to rapidly cells such as tumor cells; nondividing cells are not harmed. Several techniques have been used to introduce thera genes into tumors. Of these, virus-mediated transfer is currently the most efficient method, and the most efficient vir is the genetically engineered adenovirus. Investigators have demonstrated, using animal models, that Ad5-CD/*rep* viral transfer results in ablation of multiple types of malignancies.

This Phase I protocol is designed to study the safety of gene transfer for patients with cancer of the penis. A seconda objective of this study is to assess therapeutic efficacy. Currently, there is no standard adjuvant therapy used with partial or total penectomy . Thus, the potential risks associated with the use of gene transfer in this group would a reasonable. Patients with penile cancer will be treated with IT injection of Ad5-CD/*tk*-*rep* delivering HSV-tk . Initia

tests will use a low dose of vector. Following injection of the vector, the virus will be allowed to replicate for 1 week After 1 week, patients will begin a 2-week course of oral valaciclovir at 2 g three times daily. Only one course o therapy will be administered. Each patient will be monitored carefully for AEs. A partial or total penectomy will performed at 3 to 4 weeks after the last dose of oral valaciclovir . The primary objective of this study is to determ the dose-dependent toxicity of IT administration of the adenoviral vector in patients with penile cancer, as well as the relationship between the viral dose and the biological effects on the tumor. By monitoring patients throughout this study with a core biopsy of the penile tumor taken prior to initiating the trial, another biopsy 1 week after viral injection, and comparing these biopsies with the pathologic analysis of the surgical specimen, the impact of this therapy can be investigated.

RAC Discussion

Dr. Gordon did not initially vote for a full public review of this protocol, but his review expressed some concern abo the delay in treatment that could pose a risk to the patient. Squamous cell carcinomas generally progress very slo but he was concerned about what would happen in the interim (nontreatment) weeks if a patient experience spreading of tumor. He was satisfied with the lengthy discussion, which indicated that tumor progression is slow and the risk of spread in the space of a few weeks is minimal. Dr. Gordon was also concerned that, if a patient experience some decrease in tumor size as a result of the protocol, that patient might lobby the researchers to perform less surge on the remaining tumor, a situation that might be problematic only if the patient experiences spread of the tumor in t future. The investigators described the proposed posttransfer surgery in more detail to satisfy Dr. Gordon's concern.

Dr. Chow summarized her review by stating her major concern about waiting for prodrug treatment until 7 day postinjection , as opposed to waiting only 2 days in other protocols. The treatment delay would render normal cel susceptible to the viral replication.

Ms. King summarized her review as focusing specifically on novelty as defined broadly by Appendix M of the *NIH Guidelines*. She voted for full public review of this protocol because of questions about the risk-benefit assessment fo this disease, in which an investigational intervention is being used where a definitive but drastic treatment exists. She was concerned about the temptation to exaggerate the potential for benefit because a treatment less drastic than penectomy is highly desirable. Dr. Aguilar-Cordova's presentation was a satisfactory response about how these issues have been elaborated in the consent form. Ms. King deferred to the other reviewers' satisfaction with the 7-day treatment delay.

Dr. Kahlil's *ad hoc* written review was received only 2 days before the RAC meeting. Dr. Breakefield summariz some of his concerns, including that an adenovirus with E1B deletion may replicate elsewhere (similar to concerns expressed by Dr. Chow), that about 26 percent of these tumors have mutations in the p53 gene, and that a substantial fraction of these tumors are caused by a virus similar to a wart virus or human papillomavirus (HPV) that is i into the genome. Dr. Chow stated that penile cancer may be associated with HPV infectio

RAC Questions and Comments

Dr. Breakefield wondered whether the fact that another virus may be present in some of the tumors would make t tumors more aggressive. She also expressed concern about toxicity to normal tissues because of the likelihood of leakage into the vasculature.

Dr. Breakefield also wondered whether sexual transmission is a possibility and whether the investigators plan t monitor participants' semen. Dr. Aguilar-Cordova answered that these patients are not likely to be able to have sexual intercourse, given the location of their tumors and the fact that the size of their tumors interferes with sexual function Investigators do not plan to follow the presence of virus in spermatocytes . With regard to germ-line transmission is a completely separate blood flow pattern from that of the penis and the gonads, even though they are geographicall

near each other. Adenovirus does not integrate into the germ line, and in this particular population of patients that wi be undergoing penectomies afterward, the investigators are not concerned about vertical transmissio

In response to several RAC members' concerns about the 7-day delay in prodrug treatment, Dr. Aguilar-Cordov stated that this protocol is a two-arm approach, one of which is the replication capacity of the vector itself the cytotoxic effect of the virus. Therefore, if viral replication is shut down immediately on delivery, that part of th product becomes nonfunctional, thus defeating the purpose of having a replication-conditional (as differentiated from replication-deficient) vector. After much consideration, the investigators believe that a short period would be a reasonable approach, and they considered 7 days on the basis of their experience with 5 days in mice, in which the virus does not replicate as well as in humans. Investigators will be monitoring the patients for liver function and viremia . Most of these patients will have serum antibodies to adenovirus, so the potential toxicity is further decre because the immune system will shut it down systemically.

A FDA's clinical reviewer (name not recorded) of this protocol commented about the time delay for treatment. The FDA discussed this protocol at length during its review, and the urologist they consulted within the FDA agreed that, normally, treatment for these patients is delayed by the fact that this tumor has superimposing infections that require treatment with antibiotics to remove that infection and cool down the lymph nodes before removal. Although not as long a period as this protocol proposes, this kind of time delay is a normal occurrence with these patients so that they can be treated with antibiotics prior to surgical treatment. Dr. Aguilar-Cordova added that there is often an additional issue about treatment delay because usually the patients do not decide immediately whether they will accept penectomy as a treatmen

In response to Ms. King's concern about the ethics of using gene transfer for a disease that has a 100 percent potentia treatment available, Dr. Aguilar-Cordova stated that penectomy is still available; the protocol is in addition to th standard potential treatment.

Dr. Aguilar-Cordova stated that there is much debate about the association of HPV with penile carcinoma, and th much disagreement about whether HPV is causative at all. It is observed more frequently in basaloid carcino is not as frequently observed in squamous cell carcinom

Dr. Breakefield expressed her concern about possible dissemination of this replication-competent virus into the p domain (if a study participant is sexually active), especially if a participant is living with an immune-compromised person. Dr. Aguilar-Cordova assured her that the patients are told about specific hygiene procedures, and those recommended procedures are also included in the protocol—for example, not sharing utensils, washing hands for 10 minutes, and other procedures for preventing contamination of those around them. Virus spread is a fairly unlikely event, but patients will be advised to take standard precautions.

Dr. Gordon stated that information sent back to the RAC about biodistribution of vector after *in vivo* delivery would be useful because not many E1B deleted-only vectors have been used in the clinic. He commented that it would be interesting to see how viremic the patients become and what other tissues may be colonized by the viru

Ms. Levi-Pearl asked for clarification about the policies of the RAC in terms of a RAC member recusing himself herself when a RAC member appears to have a financial interest in a protocol under RAC consideration. Dr. Patterso explained that if a RAC member is associated with the institution where the trial will be conducted or has a financial conflict of interest, the member must be recused from the discussion and also is not allowed to vote on a protoco

Dr. Friedmann asked what is known about the environmental stability of shed adenovirus and, if it is shed, how l stays infectious and what are the recommended means to inactivate it. Dr. Aguilar-Cordova responded that, although adenoviruses are hearty, they are not indestructible. Soap and water, dehydration, or the use of bleach will inactivate the vector, depending on the length of exposure.

Public Comment

None.

Recommendations

Dr. Gordon (substituting for Dr. Mickelson, who left to attend another meeting) summarized the recommendations o the RAC as follows:

• The patients should be closely monitored including the liver function tests during the 7-day delay of initiating the valaciclovir treatmen

• Data should be collected with regard to biodistribution of the vector after intratumoral injection in or to address the issue of potential virus spread and replication.

The investigators should provide the RAC with a written response to both the reviewer's written comments, which were forwarded to the investigators prior to the RAC meeting, and to the RAC recommendations above.

No formal vote was taken by the RAC on the recommendations regarding this protocol, but general agreement was voiced on these three recommendations.

XVI. Day Two Closing/Dr. Gordon

Dr. Gordon thanked all the participants and adjourned the second day of the March 2000 RAC meeting at 6:40 p.m. on March 9, 2000.

XVII. Day Three Opening Remarks/Dr. Mickelson

Dr. Mickelson opened the third day of the March 2000 RAC meeting at 8:00 a.m. on March 10, 2000. She explained that the Working Group on Adenovirus Safety and Toxicity would be presenting an informational report that should be considered as interim, because the safety issues and information from the discussion of internally deleted adenovi vectors that occurred on Day One of this RAC meeting will be included. It is anticipated that in June 2000, this Working Group will present its final draft recommendations to the RAC for full review.

XVIII. RAC Working Group on Adenovirus Safety and Toxicity

Working Group: Drs. Mickelson and Inder Verma , Co-Chairs; Drs. Aguilar-Cordova, Ando, Breakefield , Markert , and McIvor; Drs. Bruce Chabner , Linda Gooding, Marshall S. Horwitz , Richard C. Mulligan, Nemerow , Robert Warren, Arthur L. Beaudet , and FDA Primary Contacts (Drs. Philip Noguchi and Steven E

Dr. Friedmann presented the background of the Working Group on Adenovirus Safety and Toxicity. In response SAE resulting in a death that was directly attributable to the use of a gene transfer vector, the NIH establishe RAC Working Group on October 1, 1999. Its charge is to evaluate the AdSAT data gathered from more than 7 adenovirus-based clinical trials obtained by the OBA . An AdSAT symposium was held on December 8, 199 conjunction with the December 1999 RAC meeting, at which data were assessed from a series of presentations on th biology and pathophysiology of adenovirus. The conclusion of the Working Group is that clinical trials usin adenoviral vectors should continue, with caution.

Recommendations of the Working Group include the following:

1. Standards. Qualitative, quantitative, and scientific standards should be developed to improve the comparability and value of experimental data, including vector:

- Potency (particle number, titer, dose)
- Strength (transgene expression, transduction efficiency and specificit
- Quality (identity, purity, integrity, homogeneity)
- Toxicity (standard reporting criteria)

2. Vector systems. All vector systems should be evaluated using traditional drug development approaches, including:

- Biodistributio
- Pharmacokinetics
- Target receptor distribution and concentration
- Routes and rates of administration
- Characterization of therapeutic and toxic thresholds (dose-escalation and response profiles)

3. Study controls. Whenever possible and practical, appropriate vector controls should be included in the experimental procedure, for both null vectors and deleted vectors.

4. Clinical monitoring. Patient surveillance and monitoring should occur before and after vector administration to help minimize study variability and potential acute toxicities, including:

- Patient immune status (humoral and cellula
- Predisposing or underlying conditions (patient genotype, secondary and concurrent infections)
- Patient cytokine profile

5. Informed decisionmaking . Informed consent documents should contain clear statements of risk an benefit. Patient advocates should be established to:

- Address financial conflicts of interest (investigator and institution)
- Address conflicts of commitment
- Optimize informed decisionmakin

The third-party patient advocate could be a volunteer from the IRB or the IBC, a disinterested party, o

someone from a patient advocate mechanism within the medical center.

The NIH Office of Extramural Research maintains a policy requiring a list of investigator equity stak interests that exceed $10,000.

6. Data and information. Clinical trial data (safety, toxicity, and efficacy) should be reviewed and analyzed regularly to identify trends and avenues of opportunity and highlight areas deserving further investigation.

- Data should be discussed in a public forum.

- Periodic symposia of a similar organizational design should be conducted for all gene transfer vector systems used in human clinical trial experiments.

These recommendations have been discussed within the Working Group and within the FDA, which has a 10-member working group on gene transfer research.

RAC Discussion

RAC members discussed these and other recommendations that might be added. The following specific issues were addressed during the RAC's public deliberatio

1. Presence of a third party during the informed consent process would assist patients in obtaining another opinion, hearing the same information presented in a different way, and placing the information in perspective. Investigators are usually hopeful (which results in a possible "conflict of commitment"). The purpose would be to help explain features of the research that are not in the consent form and to explain the alternative treatments. This individual would function a little differently from what is commonly referred to as a "patient advocate"; however, finding a disinterested individual who is not a member of the research team and who is appropriately knowledgeable about the protocol is quite unlikely at this stage of GTR . Some institutions use a "consent monitor," who is present at least for the part of the consen process that includes reviewing the consent form with the investigator; genetic counselors might also be able to fulfill this function. The presence of a family member during the consent process also might prove helpful for the patient. Financial support for disinterested parties should be underwritten by the research community, all of whom should contribute.

Dr. Melody H. Lin (OPRR) conveyed to the RAC that the OPRR is soon to be moved out of the and within the DHHS Secreta Office, creating a public advisory panel for the first time; this new advisory panel would be an appropriate forum for suggesting a policy related to use of a disinterested third party in the consent process. Recommendations for enhancement of the informed consent process at the present time could emanate from the National Bioethics Advisory Commission, to which Dr. Macklin is a consultant.

Ms. King enumerated some of the differences and similarities between GTR and other protocols tha relate to the consent process. Differences include a high concentration of conflicts of interest and commitment and public perceptions about GTR . Similarities include subjects who are particularl vulnerable and dealing with highly technical information.

2. There may be a need to establish institutional conflict of interest rules. Investigators could have significant equity holdings in a relevant company.

3. Investigators and sponsors should work to increase the comparability of ongoing studies by developing industry standards for viral vectors. The FDA may not be able to accomplish this task alone; the RAC could assist. Standardization among laboratories would allow a broad examination of safety issues. Dr. Ando suggested that the NIH National Gene Vector Laboratory could play a role in developing thes standards.

4. It may be confusing to patients to call a virus a "drug." Patients need to know that there is a chance that the virus will replicate and that it is possible that the virus could integrate into the genome, both of which a drug cannot do. Dr. Breakefield reminded the RAC that serious issues exist as to the possible spread o the vector to other individuals when using replication-competent vectors.

5. The field would benefit from model informed consent forms and agreed-on statements and statistics. Ms. King suggested that RAC members review Appendix M-III (of the *NIH Guidelines*), which lays out the elements of the informed consent for GTR , to determine whether it is extensive enough and whether i includes the kinds of concerns that were expressed during this RAC discussion.

6. Dr. Breakefield wondered whether infectivity in animals is the same as infectivity in humans an whether it is appropriate to translate doses only by body weight. This information would assist the GTR field in evaluating the safety of different vectors.

• Many basic biology issues about adenoviruses remain unknown. Dr. Breakefield state that, if gutted viruses are posited as being safer, the GTR field needs to know whether a empty adenovirus virion is toxic or not. She also recommended that the data surroundin Jesse Gelsinger's death be analyzed by someone who would then provide a best guess about exactly why this death occurred. Dr. Markert suggested that the RAC request a follow meeting with Dr. James Wilson, University of Pennsylvania, who could discuss any additional findings since his report at the December 1999 RAC meeting. Dr. Gordon stated that collecting needed information systematically will allow the GTR field to identify peopl who may be at especially high risk for SAEs ; this Working Group was assembled t recommend the systematic efforts needed to benefit patients and the public. Dr. Ando noted the additional need for systematic application to other investigators of the information that is newly acquired.

Dr. Markert suggested that, when the RAC receives protocols involving adenovirus, a shor list of suggestions should be e-mailed to the investigators to contemplate data acquisition if they have not already done so. At a minimum, that list should include measurement of cytokines and the cellular immune response to adenovirus.

9. Dr. Friedmann noted that the RAC discussion at this meeting grew from focusing on the general issu of adenovirus toxicity and safety to a focus on information flow and advocacy. He pointed out that the RAC has an obligation to present policy conferences, the next one of which could focus on information flow and identification and resolution of safety issues. The issues of safety as they relate to consent and to the design of studies and how these issues are presented within the GTR community and to the publi and to patients represent a knowledge and discussion void. A policy conference on this issue would catalyze the public discussion.

Dr. Mickelson suggested that any additional comments be e-mailed to her.

Public Comment

Dr. Savio L.C. Woo, American Society for Gene Therapy (ASGT) and Mount Sinai School Medicine

Dr. Woo stated that the ASGT leadership has held many telephone conferences in recent months to deal with th issues surrounding Jesse Gelsinger's death. Standardization of gene transfer vectors is evolving and will be a continuous issue as new technologies are born. In anticipation of standardization, the ASGT will conduct fiv workshops at its annual meeting in Denver in June 2000, one each on adenovirus, AAV , retrovirus, lentivirus lipoplexes . These workshops will examine technical aspects such as production, scale-up, formulation, an purification. Everyone in the field is invited to participate under the condition that everything said will not be proprietary for any reason. The goal is to disseminate information to the public and to the ASGT membership. D Breakefield will present an education session on the clinical aspects of GTR , co-moderated by Dr. Noguchi a Patterson, to disseminate information to ASGT members about the intricate guidelines of how to conduct clinica research and protect patient safety. The workshops will be open to the full ASGT membership, and summaries m available on the ASGT Web sit

Mr. Paul Gelsinger , father of Jesse Gelsin

Mr. Gelsinger confirmed that patient advocacy is an important issue and that it is universally lacking. A nationa center, maybe through the NIH , would be useful and would need to be headed by someone who is intimately fam with GTR . Such a program should be funded by researchers, and all should contribute financially. Potentia participants and their families should be encouraged to use such a resource. As an example of this need, Jesse's referring physician did not have the appropriate knowledge about the OTC trial.

Potential participants should have access to all vested interest statements and should be able to read the complete protocol, not merely the consent form. These "needs" do not apply only to gene transfer but are a national issue for a research.

Ms. Beth Hutchins, Canji In

Ms. Hutchins stated that the companies involved in GTR will be sponsoring a symposium at the ASGT ann meeting to discuss advenovirus standardization. This symposium is intended as a kickoff to augment interest an involvement in a full-day workshop planned for the future. The FDA is involved in planning the workshop, and the OBA will be kept informed about i

Dr. Stewart Newman, New York Medical College and Council for Responsible Genetics

Given concerns about vector use and Dr. Woo's proposal to explore standardization, Dr. Newman asked why there is a desire to continue trials until standardization is available. Dr. Mickelson requested that discussion of this request be deferred until the afternoon, during Mr. Rifkin's presentation.

Mr. Jeremy Rifkin, Foundation on Economic Trends

Mr. Rifkin reminded the RAC that there were warnings 10 years ago that viral vectors could cause potential health problems, that conflict of interest could occur with companies involved in GTR , that insufficient preclinical resea had been done, and that protocols were not in place. The minutes from the December 1999 RAC meeting reflect questions that should have been asked 10 years ago. Autopsies on patients should always be conducted. There was no reason for Jesse Gelsinger to die, and there is no reason for any unaccountable deaths. Questions about reporting accountability, and consent forms should have been dealt with 10 years ago.

XIX. Discussion of Human Gene Transfer Protocol #9910-345:*A Phase I/II Dose-Finding Trial of*

the Intravenous Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, Patients With Hormone-Refractory Metastatic Prostate Canc

Principal Investigators: Dr. George Wilding, University of Wisconsin Medical School

RAC Reviewers: Drs. Breakefield and Markert and Ms. Levi-P

Ad Hoc Consultant: Dr. Kamel Khalili , Temple University (written rev

The principal investigators provided a 15-minute presentation of their protocol, the reviewers discussed their concern (with time allotted for responses), and the RAC and the public presented additional questions.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were eithe unresolved or novel and that the protocol warranted public discussion. These issues included: 1) a safety concern of intravenous administration of a replication-competent virus for prostate cancer patients, who may be immune compromised; 2) a concern of the potential for virus replication in non-target tissue; 3) a concern about biodistribu of the virus following intravenous administration over time; and 4) a concern that the virus containing the prostate specific antigen promoter, which regulates the E1 and E2 genes, may render this variant adenovirus to have greater tendency than the wild type virus to propagate in the prostate and to spread to other tissues and to other individuals. Such preferential replication in the prostate gland and virus spreading may have potential to cause sterility and toxic effects to other tissues.

Drs. Breakefield , Markert , and Khalili and Ms. Levi-Pearl submitted written reviews, to which the invest responded in writing. Major concerns expressed in the written reviews included a variety of informed consent form issues (the form was modified extensively by the investigators as a result of RAC review); presence or absence of antibodies to the adenovirus and the relationship to dose escalation; ensuring compliance with the stopping rule of th protocol; cytokine levels triggering a possible change in trial implementation; vector transfer through sperm (investigators reported that this patient population will have been previously castrated, either surgically or by hormon manipulation); possible mutations in the virus genome; characterization of the specificity of prostate-specific promoters; preclinical studies in nonhuman primates; assessment of immunocompetence of patients; studies usin larger cohorts of cotton rats to provide better assurance and significance; and the relative increased risk to patients of an E3+ replication-competent vector.

Protocol Summary

Prostate cancer is the second leading cause of cancer death in men in the United States, with more than 39,000 deaths in 1998. The incidence of this cancer has increased dramatically during the past 25 years, which is attributed in part t improvements in screening for elevated prostate-specific antigen (PSA). Although elevated PSA levels some represent the natural phenomena of aging or of other physiological states, they continue to be the most useful marker for malignant disease.

If prostate cancer is caught early it can often be cured, but if the disease metastasizes and continues to progress, curre first-line chemotherapy is not generally curative, and therapy is usually aimed at palliation and pain control using a variety of agents. However, if patients fail these regimens, currently there is no further therapy that can be offered. New therapeutic modalities are therefore actively being sought for these patients.

The proposed trial is aimed at patients in whom the cancer has spread and is based on the use of an adenovirus that has been altered by inserting it with promoter and enhancer elements cloned from the human PSA gene. As a res

this engineering, Calydo's new therapeutic attenuated replication-competent adenovirus ARCA reproduces in prostate cancer cells (or those cells containing PSA), causing cancer cell death. ARCA affects a minute numb cells that do not contain PSA (10,000:1), thus limiting the death of noncancerous ce

Starting in 1996, in experiments in mice, a single injection of Calydo's viral therapeutic CN706 caused implanted tumors to shrink by an average of more than 80 percent. At the same time, PSA dropped to undetectable levels. dose-finding experiment in the same animal studies showed increasing tumor shrinkage as the dose of CN706 was increased. No significant side effects appeared in the treated animals, and the cancer did not reappear.

Human studies on the first-generation virus CN706 began in 1997 at the Johns Hopkins University Oncology Center. This study showed promising results when virus was injected directly into the prostate of patients with localized disease. A second generation of the ARCA virus, CV787, was developed by Calydon in 1998. In animal stud new product showed much higher effectiveness in destroying cancer cells, while maintaining a record of insignifican negative side effects.

The proposed clinical study is a multicenter , open-label, dose-finding study of CV787 adenovirus in patients wit hormone-refractory metastatic prostate cancer. The primary objectives of the study are to determine the safety tolerance, and maximum tolerated dose of CV787 administered intravenously to patients with metastatic hormone-refractory prostate cancer. Secondary objectives are to evaluate the PSA response rates, duration, and ti progression in these patients; evaluate other observed clinical efficacy responses; evaluate the systemic pharmacokinetics of CV787 administered intravenously; and monitor the immune response to CV787. Up to 48 patients will participate in this study. CV787 will be administered by IV infusion in 10 mL volume over 10 minu with overnight hospital stay, weekly followup for 1 month, and followups at months 2, 3, 4, 6, 9, 12, 15, 18, 24. PSA response and progression, safety, immune response, and systemic bioavailability and biodistribution monitored.

RAC Discussion

Dr. Breakefield began the summary of her review by stating that the compa's responses to the RAC reviewers' comments were extensive and produced confidence that the researchers are moving ahead carefully. On the issue of safety, most RAC members believe that germ-line transmission is not a concern. The toxicity level related to this vector might be warranted, given the seriousness of this disease. Animals have been held for only 22 days to test for the presence of additional viral replication; Dr. Breakefield recommended that they be held longer before conclu that the virus is not replicating. She also recommended that the investigators inject this virus directly into the brain o nonhuman primates to determine whether the virus gets into the brain and whether there is a population in the brain, which is an immune-privileged site, that will support the replication of this virus. Dr. Breakefield noted that this is similar to the wild type adenovirus, containing all the viral genes, especially the E3 gene that allows the virus to evade the immune system and assume latency in lymphocytes, with no gene available to stop its replication. In addition, the vector is being administered intravenously. Prostate promoters should limit the virus to the prostate, but such a result is not guaranteed.

Dr. Markert stated that the investigators responded completely to the comments and questions from her review. I specific response to discussions held at the December 1999 RAC meeting regarding Jesse Gelsinge death, the investigators will measure a variety of interleukin levels, and the issue of the initial titer of antibody to adenovirus wi be standardized, so that all patients have a low level of antibody within the dose escalation, thus significantly reducin the possibility of a similar SAE

Ms. Levi-Pearl concentrated her oral review on the changes in the informed consent form between the original and revised versions. The revised form is significantly shorter, and a considerable number of changes have occurred in th consent form between the two versions. For example, the question-and-answer (Q&A) format in the first version was

eliminated, a statement about the death of Jesse Gelsinger was removed, and several risks outlined more complet the first version were less well explicated in the second version. In addition, the consent form should contain information on animal data and an autopsy request. Ms. Levi-Pearl provided to the investigators a list of the items in the first iteration of the consent form that are missing in the second version and should be reinstated.

RAC Questions and Comments

Dr. Greenblatt queried the investigators about the oncology commu's acceptance of PSA response as a surroga for tumor response. Dr. Wilding acknowledged that the PSA response is an indication of what is going on in pros cancer. In a situation in which researchers believe there is a cytotoxic effect on the cells, and therefore that th numbers of cells may be diminished with some kind of therapy, the clinical community believes that PSA can be to correlate to a positive effect on the disease. Although the FDA does not recognize PSA as an endpoint fo registrational studies for prostate cancer, PSA is a useful tool for Phase I and Phase II studies as a potential su marker (not as a measure of the absolute cancer volume). The investigators in this protocol recommend that 50 perce over a series of multiple PSA evaluations should be considered a partial respons

In response to Ms. Levi-Pearl's concerns about the consent form, Dr. Wilding explained that the changes to the form were in response to comments from the IRB and that Jesse Gelsin's death is mentioned on the revised form, although not by name.

Dr. Friedmann expressed his concern that the use of the term "cold virus" to describe the adenovirus may reduce relevance of patients' concerns. The common cold is caused by a rhinovirus. The current wording suggests that if something goes wrong, a patient will "just get a cold." Dr. Wilding explained that that term represents an attempt to put the adenovirus into context for patients who do not know the classifications of viruses; he agreed to eliminate tha reference in the consent form.

Dr. Friedmann noted that, if a variant were tropic to another tissue and infection of that tissue could be deleteriou investigators would use repeated exposures in multiple cycles to find that variant. Long-term animal studies might be warranted to look for evidence of the emergence of variants with different tropisms. Dr. Daniel R. Henderson, Calydon , responded that animal experiments would be feasible but believed them not necessary because of th experiences of millions of military service personnel being exposed to adenovirus vaccines. Dr. Pilaro added that are human viruses that do not replicate in nonhuman primates; wild-type virus will only replicate (and to a limited extent) in cotton rat lung.

Dr. Gordon expressed concern about the ability of this virus to penetrate a tumor mass, since it is supposed to penetrate relatively poorly. Dr. Henderson assured the RAC that animal studies indicate that penetration of the tumor does occur—although approximately 90 percent of the virus in the rodent models went to the liver, the remainder of the virus goes to the distant tumor and penetrates it. In addition, prostate cancer metastasizes preferentially to bone marrow, which has fenestrated capillaries and has an ability, because of the resulting large spaces, to pass adenovirus as a particle into that environment.

Dr. Aguilar-Cordova wondered how long this vector continues to replicate and how soon after injection the observed leakage occurred. Dr. Henderson responded that the initial peak of vector replication is in eclipse by 24 hours, followed by a secondary peak within 3 to 8 days. The secondary peak correlates inversely with the level of preexister antibody prior to treatment; however, that peak does not last longer than 8 days, and the researchers have seen no replication past that point. IT injection of $1x10^{10}$ particles followed through the first hour (using the mouse xenogra model) showed a rapid drop of available virus in the bloodstream and a leakage of about 0.1 percent that appears to hold constant.

Dr. Breakefield suggested that, since animal models appear to be unavailable and therefore humans are the bes

"model," it is important to monitor tissues in addition to serum and urine, specifically stool and saliva. Dr. Henderso responded that there are too many inhibitors in stool to provide a quantitative answer, but that saliva might be possib He noted that the only reports of PSA production in any other tissue come from saliva, at 1/10,000 the level o PSA -producing cell

Dr. Mickelson summarized the discussion by noting the following recommendations and comments:

- Researchers should extend animal studies to more than 22 days.
- Promoter stability in animals should be examined.
- Concrete suggestions for improving the informed consent form were offered, and investigators agreed to attempt to return to the Q&A format.
- The description in the revised consent form of the University of Pennsylvania protocol is sufficient.
- Additional discussion of preclinical data is needed.
- Postmortem examination results of all participants should be requested.
- Researchers should conduct more permissive nonhuman primate studies to determine whether there is a pocket in which the virus might replicate, other than the prostate and the prostate tumor.
- Shedding should be tracked in the saliva, urine, stool, etc. to obtain a better idea of the extent of replication competence.

Public Comment

None.

Committee Motion 1

A motion was made by Dr. Breakefield and seconded by Dr. Markert to extend patient monitoring for the pre virus in saliva and other body fluids over extended periods after injection in order to observe any likelihood of emergence of replicating virus. The motion passed by a vote of 12 in favor, 0 opposed, and 1 abstention.

Committee Motion 2

A motion was made by Dr. Breakefield and seconded by Dr. Friedmann to request that the investigators use r mice or another type of animal to check other tissues for replication of variants from the vector population. This motion failed by a vote of 4 in favor, 7 opposed, and 2 abstentions.

Committee Motion 3

A motion was made by Ms. Levi-Pearl and seconded by Dr. Gordon on several items regarding the consent form. (1) The original question and answer format used in the University of Wisconsin Medical School consent form is preferable than the revised form. (2) The informed consent form should include extensive discussion of preclinical animal data and its implications for clinical risk and benefit. (3) A request for autopsy should be included. (4) The sentence in the last page of the informed consent document should read: "You are free to consult with your personal

physician if you would like an independent second opinion." The original quotation marks used for the phrase "second opinion" should be removed and an additional word "independent" be added to emphasize the role of such a opinion in the informed consent process. This motion passed by a vote of 12 in favor, 0 opposed, and 1 abstention.

XX. Discussion of Human Gene Transfer Protocol #9908-337: ***Transduction of CD34+ Cells From the Umbilical Cord Blood of Infants or the Bone Marrow of Children With Adenosine-Deaminase -Deficient Severe Combined Immunodeficien***

Principal Investigators: Dr. Donald B. Kohn, Children's Hospital, Los Angeles

RAC Reviewers: Drs. Markert , McIvor, and Ms. Ki

The principal investigators provided a 15-minute presentation of their protocol, the reviewers discussed their concern (with time allotted for responses), and the RAC and the public presented additional questions.

Background

During its preliminary review of the protocol, the RAC determined that a number of issues in the protocol were eithe unresolved or novel and that the protocol warranted public discussion. These issues included: (1) the informed conse document not describing one available, standard, successful, and alternative therapy, i.e., half-matched T-cell deplete bone marrow transplantation without chemotherapy; (2) a concern about the use of PEG-ADA which would potentially remove the treatment option of bone marrow transplantation (without chemotherapy); and (3) a special concern about enrolling infants or children in this protocol.

Drs. Markert and McIvor and Ms. King submitted written reviews, to which the investigators responded in writin Major concerns expressed in the written reviews included the problem of not offering bone marrow transplantation without chemotherapy; contents of the vector and whether the regulatory region in intron 1 of the adenosin deaminase (ADA) gene has been included; an additional safety issue about whether patients are at risk to continu low levels of polyethylene glycol-conjugated bovine adenosine deaminase (PEG-ADA) if antigen-specific respo fall; risk-benefit concerns and the justifiability of this protocol given the current status of allogeneic stem cel transplantation for this disease; whether participation in this protocol would preclude a subsequent half-matched transplant without chemoablation ; the importance of IRB approval of the consent form as revised; and maxi subject age for those diagnosed postnatally who will be enrolled in arm 2 of the stud

Protocol Summary

The enzyme ADA is needed for T and B cells of the immune system to develop. Children who are born with mutations in the ADA gene and who do not make ADA enzyme have severe combined immunodeficiencey (SC Children with SCID generally die in the first year of life from severe infections because their immune systems ca fight infection. SCID can be cured by a bone marrow transplant, but this is an imperfect approach because man children do not have siblings who are tissue matches to serve as bone marrow donors. Transplanting bone marrow from a parent who is only a half match or from a nonfamily member can lead to significant problems, from reject the bone marrow graft to reaction of the donor's immune cells against the SCID patient. There is an effective form enzyme therapy (PEG-ADA) for ADA-deficient SCID , in which children receive injections of purified ADA enz once or twice each week. ADA enzyme injections allow the immune system to recover to a level that protects the child from infections. However, these injections must continue throughout life, or immunity will wane. ADA enzym therapy is expensive, costing from $100,000 to $300,000 annually.

Gene transfer for ADA-deficient SCID could be performed by introducing a normal copy of the human ADA ge into the patient's blood-forming stem cells, which are then transplanted back into the patient. Stem cells are present i

bone marrow and also in the umbilical cord blood of newborns. Effective gene transfer for ADA-deficient SCID requires inserting the normal human ADA gene into a sufficient number of the subject's stem cells and expressing the gene to make ADA enzyme in the subject's immune blood cells.

In this study, investigators will determine whether this gene transfer approach is safe, feasible, and effective. They w treat 10 subjects, either newborn infants diagnosed prior to birth or children with ADA-deficient SCID . Umbilica cord blood and bone marrow will be collected from the infants at birth and during childhood, processed in the laboratory to introduce the normal human ADA gene (using retroviral vectors for gene delivery), followed by return of the cells to the subjects by IV infusion. Two different ADA gene vectors (GCsap -M-ADA and MND -ADA differ in transcriptional control elements) will be used side by side to determine whether one works better than the other. The infants will be started (and children maintained) on ADA enzyme therapy because it is a known, effective therapy. Investigators will examine blood samples taken monthly for the next 2 years to evaluate whether there are side effects of the procedure, whether the new ADA gene is present in blood cells, and whether the new ADA gene is working to make ADA enzyme. If researchers determine that the ADA gene is present and active, they will wean the child from ADA enzyme therapy to determine whether the gene delivery has produced enough corrected cells for the immune system to be protective without the need for further enzyme injections. In summary, this trial will use new methods and new vectors, compare bone marrow in children to cord blood in infants, compare two retroviral vectors differing in transcriptional elements, and have a planned PEG-ADA withdrawal if sufficient ADA gene transfer and expression have occurred.

RAC Discussion

Dr. Markert stated that this protocol was carefully conceived. Her main concern related to ensuring that the infor consent form adequately addresses available alternative therapies; the other issues enumerated in her review were answered by the investigators. ADA-deficient SCID has several possible therapies, aside from enrollment in thi protocol, for patients who do not have sibling donors with identical human leukocyte antigen. Regarding the use of haploidentical matched, T-cell-depleted bone marrow transplant from a parent, results published in 1999 in the *New England Journal of Medicine* indicate a success rate of 60 to 80 percent, and it does not involve chemotherapy. Her concern was that, if gene transfer were not effective, these patients would not be able to safely receive a bone marrow transplant because they would have to be withdrawn from the PEG-ADA required for this protocol so their immune system function could be reduced to zero (to avoid rejection of the transplant). Despite her misgivings, Dr. Marker would like to see the protocol go forward as long as the issue of alternative therapy is covered sufficiently in the informed consent form.

As in her review, Ms. King addressed the issue of risk-benefit assessment for an investigational intervention for a condition for which several other reasonably successful treatments exist. She raised two principal ethical concerns: (the temptation to exaggerate the potential for direct benefit from participation, because of the hope that this protocol will yield a better alternative, and (2) the possibility that participation in this protocol would preclude the use of the best currently available treatment. The investigators responded to those concerns by revising the consent form, which has not yet been approved by the IRB . Ms. King stated her belief that the consent form and process should promo self-scrutiny of investigators' hopes and beliefs to best facilitate informed decisionmaking by patients and familie especially because of the existence of a wide range of treatment and research options and because this is a Phase I study.

Dr. Markert expressed concern about discussion of PEG-ADA and the possibility of haploidentical bone mar transplantation in the consent form. Dr. Michael Herschfield , Duke University Medical Center, explained that he consultant to the company that makes PEG-ADA and receives a grant from that company to monitor the treatment of patients receiving PEG-ADA worldwide. PEG-ADA is an effective therapy that could be offered to patients by their physicians as an alternative to haploidentical bone marrow transplantation. Dr. Herschfield explained that the been 60 patients treated with PEG-ADA in the United States and Canada in the past 14 years, 51 (85 percent) of

whom are still alive and 46 (77 percent) of whom are still on PEG-ADA. Thirty-seven of those patients have been treated for longer than 2 years, for an average of 7.5 years and a range of 2 to 14 years. Of the five deaths (8 percent) among patients while they were receiving PEG-ADA, none appeared directly related to PEG-ADA, making it comparable to any series of haploidentical bone marrow transplantation. Dr. Herschfield stated that, on exam all the issues for newly diagnosed patients with ADA-deficient SCID , each of the therapies that might be chosen impact the potential for using the others.

Dr. Wolff queried Dr. Herschfield about his assessment of how long a patient would have to wait after withdrawa from PEG-ADA for the plasma level to decline to zero. Dr. Herschfield responded that 16 patients worldwide ha been treated with PEG-ADA longer than a month, were withdrawn within 3 months to 5 years, and then went on to bone marrow transplantation. Although the information is not published, the time course has been followed in severa of those patients, indicating that it takes 2 to 3 weeks before the level of PEG-ADA in plasma declines to zero, at which point immune deficiency begins. Regarding Dr. Wolffs question about the risk to patients of this 2- or 3-week wait, Dr. Herschfield responded that the period of risk is no longer than it is for doing a haploidentical transp newly diagnosed patient, in part because such patients often present as critically ill and time is needed for stabilizatio

Ms. King expressed her concern about conflicts of commitment that might impede the informed decisionmaking process by becoming persuasive rather than fostering an information exchange that allows parents of subjects to mak the best informed decision about participation in Phase I research. It is important to make this issue a part of the informed consent document.

Dr. Markert reviewed the revised consent form and noted that all RAC suggested changes had been incorporate

Public Comment

None.

Committee Motion

A motion was made by Ms. King and seconded by Dr. Gordon that the RAC found the revised informed consent document addressed all the RAC concerns and recommended that Institutional Review Boards at both clinical trial sites, i.e., the Childrens Hospital Los Angeles and the NIH Clinical Center, accept the revised informed cons document. The motion passed by a vote of 11 in favor, 0 opposed, and 1 abstention.

XXI. A Member of the Public: Proposal for Moratorium on Some Human Somatic Gene Therapy Protocols Using Viral Vectors

Working Group: Ms. King, Chair; Drs. Ando, Breakefield , Juengst , Markert , Mickelson, and Wolff an Levi-Pearl

In a letter dated November 22, 1999, Mr. Jeremy Rifkin, Foundation on Economic Trends, requested that the RAC consider imposing an immediate moratorium on the consideration of any future human somatic gene transfer protoco that employs retroviral, adenoviral, or other viral vectors, except where the protocol can legitimately be considered a treatment of last resort for a life-threatening illness. A RAC Working Group prepared a draft response to the proposa and notice of this agenda item was published in the *Federal Register* on February 18, 2000 (65 FR 8618). The proposed amendment to the *NIH Guideline* reads as follows:

> "Given the recent death of a patient undergoing somatic gene therapy at the University of Pennsylvania and the disclosure of six other deaths involving patients undergoing gene therapy, the Foundation on Economic Trends is formally requesting that the National Institutes of Health Recombinant DNA

Advisory Committee (RAC) vote to impose an immediate moratorium on the consideration of any future human somatic gene therapy protocol that employs retro-, adeno -, or other viral vectors, except where th protocol can legitimately be considered a treatment of last resort for a life threatening illness."

Overview of Proposal

Mr. Jeremy Rifkin, Foundation on Economic Trends

Dr. Stewart Newman, New York Medical College and Council for Responsible Genetics

Mr. Rifkin and Dr. Newman provided an overview of the moratorium proposal. Ten years ago, Mr. Rifkin raised a number of issues regarding GTR : insufficient preclinical research, serious potential complications using viral vec as media, inherent conflicts of interest so great as to bias the safety of protocols, and regulatory procedures that were insufficient or inadequate. Currently, there is one known death, several unaccountable deaths, and hundreds of AE reports. Conflict of interest is a fatal flaw of the process because, although researchers are expected to report results, reporting may not be in the best interest of the company for which those researchers work. Thousands of patients hav participated in 300 experiments, but not one cure has resulted.

Proposed is a moratorium on all gene transfer experiments involving viral vectors except in cases of life-threatening illnesses; trials should be allowed to continue for last-resort patients. If data in these trials show increased safety and less toxicity, those data can be used to suggest how to proceed to the next less serious category of illness.

Little is known about how adenoviruses and other viruses affect patients, and AE reports have not been examined to determine whether the viruses are implicated in those AEs. Autopsies have not been performed on most of the patien who have died to determine whether the gene transfer caused the problem that resulted in death. With so many questions and few answers, patient interest dictates that patients should be protected from being exposed to risk.

Phase I trials should be redefined to include only patients who need to benefit from the protocol because they are dealing with life-threatening diseases. Only people whose health is significantly compromised should participate. Evidence could still be gathered, although not as quickly, and animal models could be used concomitantly to predict which vectors might help correct the condition.

Mr. Rifkin reiterated that a moratorium should be enacted until appropriate protocols and additional safety nets exist. Patient interests may not be protected adequately by the FDA or the RAC. The RAC has the responsibility and the opportunity to do the "right thing" by imposing this partial moratorium. When appropriate protocols are in place, regulations are worked out, and viral vector problems are known, then research can move more aggressively. If this moratorium is not enacted, some subjects may die, and others may be harmed.

Dr. Newman reviewed some of the uncertainties in using viral vectors in protocols that turned up in the discussions from the December 1999 RAC meeting: uncertainties in biodistribution relative to the routes of administration whether IV or intra-arterial; the relationship between the immune status of the individual and the efficacy of the viral transduction; quality control of the vectors; evidence of mutations between different lots of supposedly identical vectors; and nonlinearities in dose response relative to toxicity effects in animals and in human nonfatal SAEs . U volunteers who have the disease in Phase I toxicity/safety trials entices people to participate in these protocols, as it d Jesse Gelsinger . It also provides the investigators with a loophole, because the patients are ill to begin with AEs can be blamed on the underlying condition directly or on the medication related to that underlying condition.

Dr. Newman advocated that the viral vector clinical trials be made available only to people whose health is seriously compromised. If these people are helped, evidence should be gathered and, without trade secrets, shared. Science can proceed under such circumstances, and useful data can be gathered. When information is available, from AEs and

autopsy results, it can be shared among different groups and used to refine the protocol. At the least, the people who are the subjects of these protocols will have the possibility of being helped by them.

Working Group Report/Ms. King

Ms. King stated that discussion about this proposed moratorium presents an opportunity to summarize a wide range o scientific and policy issues. She circulated articles on the history of the RAC, public perception, and the difficulty of conveying information appropriately. The RAC is one of many players in the field of research oversight and has a long history of attention to these issues. Much guidance about how to engage in oversight already exists. Some issues have not been addressed completely because they surface and resurface. Regulatory and legislative guidance has bee available, and there has been increasing emphasis on improving investigator training.

The Working Group pared down their charge to two questions:

1. Is a moratorium on gene transfer protocols using viral vectors in humans appropriate at this time?

2. Is an exception for a "treatment of last resort for a life-threatening illness" appropriate at this time?

The Working Group answered "no" to both questions.

Activities in progress to improve safety and strengthen oversight in GTR with human subjects include the follow

- Working Group on Adenovirus Safety and Toxicity report and recommendations

- Working Group on Current Issues in Adverse Event Reporting report and recommendations

- NIH Director's Office anticipated signoff on the amendment to the *NIH Guideline* regarding protocol submission timing and initiation of subject enrollment

- Site visits initiated by the NIH Office of Extramural Resear

The real challenge is the question of attribution. Guidelines currently require all SAEs to be reported immediatel

Recommendations to improve safety and strengthen oversight in GTR with human subjects include the followin

- Increased attention to risk information in RAC review and recommendation of protocols for full review and public discussion

- Formation of an NIH /FDA working group to examine the feasibility of creating a DSMB for all g transfer research

- Improved education of IRBs , investigators, and institutions about the nature and content of the *NIH Guidelines*, especially Appendix M ("Points to Consider") and OBA /RAC availability to provid guidance and advice

- Increased attention to other available monitoring mechanisms that can be undertaken at research sites

The RAC can be more useful to IRBs than it has bee

On the basis of the above reasoning, the Working Group recommended continuation of a case-by-case analysis of protocols. The RAC shares public concerns about risks to subjects, but those risks can be addressed on a basis that allows for more flexibility than a moratorium. With exceptions for treatment of last resort, an enormous tendency would exist to overpromise the benefits of early-phase clinical trials. This tendency cannot be meaningfully addr or solved by making an exception for the most seriously ill patients. It is necessary as well as possible to protect research subjects.

The compassionate use argument is often overused; it is not enough reason for someone to be dying with no other hope, because only in Phase III is there a reasonable expectation of possible benefit. Use of a "treatment of last resor exception under these circumstances is likely to promote inadvertent exploitation of vulnerable subjects, without increasing the likelihood of benefit to them or of contributing to generalizable knowledge. Enrollment decisions these circumstances should reflect the duty to minimize risks to subjects and gather data that can help determine whether the intervention being studied is safe and effective. Enrollment of both seriously ill patients as subjects and patients with less serious disease is appropriate in GTR , as long as risks are minimized and there is adequate disc and informed decisionmaking

The Working Group recommended that the RAC:

- Vote to reject the Foundation on Economic Trends' proposal and decline to propose any action to amend the *NIH Guidelin* on the basis of that proposal

- Endorse this Working Group statement to reflect (1) the RA's belief that the many current, proposed, and recommended efforts to improve safety and strengthen oversight in GTR are sufficient and (2) th RA's desire to see these efforts go forwar

Mr. Rifkin responded to the Working Group presentation by stating that the point of the proposed moratorium is, given that experts appear to know so little (which he concluded in part from a reading of the December 1999 RAC symposium/meeting minutes), that none of these patients should be guinea pigs, especially to pursue the self-interest corporations financially involved in the research. However, if people want to participate altruistically to advance this potential therapy and clearly understand all the benefits and drawbacks, they ought to have the right to do so.

RAC Discussion

Dr. Gordon stated that the Working Group deserves credit and respect for sorting through this challenging problem. The RAC should not issue a written report, primarily because issues brought forth by the public historically have not received a RAC written response. Public discussion at this RAC meeting is sufficient.

In some cases, trials are more appropriately conducted on earlier stages of a disease; for example, in breast cancer when large tumor loads are present, it may not be possible to ascertain efficacy. Amyotrophic lateral sclerosis (AL another disease for which it would not be possible to test end-stage GTR effectiveness. There are many other sim examples indicating that GTR effectiveness on advanced disease would not be at all informativ

Public Comment

Mr. Charles Rogers, patient in cancer protocol

Mr. Rogers stated that he is a survivor of cancer. He started with chemotherapy and radiation aggressively to kill tumors in both lungs. It was a difficult course of treatment, and the tumors recurred. Surgery was not possible. The researchers with whom he dealt had no financial interest in his therapy but were interested in the possibility of saving lives. Gene transfer was the greatest hope he could find, although he expressed deep regret about the difficulties now

surfacing in the GTR field. After three injections, biopsy showed that the cancer cells were killed and 98 percent the tumors were gone. Mr. Rogers stated that he remains a supporter of GTR

Mr. Stephen Bajardi , National Hemophilia Foundation (NHF) and National Organization of R Disorders (NORD

Mr. Bajardi stated that the NHF and the NORD represent thousands of people with rare diseases across th The NHF and the NORD recommended not approving the moratorium under consideration. A moratorium w stimulate anxiety throughout the country. Many worthwhile experiments are going on; there is no need to stop all of them at this time.

Constituents can be protected by giving them information, which allows informed decisionmaking . Good science safety can exist simultaneously. The NHF and the NORD recommended that the FDA and the RAC reach ag on reporting AEs. New processes and new procedures that bring good science to a halt is not an appropriate solution. The NHF and the NORD are committed to working with the RAC to help this become a high-quality dialog. safety, reporting of AEs, and proper oversight can be resolved without stopping the development and movement of good science. If these trials are stopped, many more "AEs" will occur.

Mr. Michael J. Werner, Biotechnology Industry Organization (BIO)

Mr. Werner explained that BIO represents more than 900 companies and centers engaged in biotechnology research. This moratorium proposal is ill advised and short sighted, it will delay vital research, and adoption of it will cause more harm. Several gene transfer products have shown safety and are beginning to show efficacy. Scientific and medical discoveries take years and decades to prove safety and success (e.g., monoclonal antibodies). GTR is sul to greater oversight than almost any other area of research.

A responsible oversight system is important; BIO has proposed one, and the industry is willing to provide data to the RAC and to the OBA contingent on an agreement between industry and the NIH that would standardize how would be used. A useful first step would be an analysis and report of data from gene transfer protocols to determine the nature and extent of AEs that have occurred and how they have been addressed. The promise of GTR has not been realized, but data are encouraging. Patients with these conditions need access to these research trials. Mr. Wern emphasized that a moratorium would halt a promising area of research and would hurt, not help, patients.

Mr. David Nance, Introgen Therapeuti

Introgen is involved in 17 completed and ongoing studies. Ad-p53 is perhaps the safest drug with which cance researchers have worked, and it is demonstrably less toxic than many other currently available therapies. GTR sh not be stopped; these trials are important to patients. Complete disclosure would take care of the conflict of interest problems. Progress is being made. The RAC should interact freely with colleagues at the FDA.

Committee Motion

Since no motion was brought to the floor, no vote was taken on this proposal or the Working Group statement.

XXII. Chair’s Closing Remarks/Dr. Mickelson

The Working Group on NIH Oversight of Clinical Gene Transfer Research will be on the agenda for the June 20 RAC meeting. The Working Group on Adenovirus Safety and Toxicity will continue its work and prepare a draft report proposal for the June 2000 meeting. The Working Group on Current Issues in Adverse Event Reporting will continue its deliberations; Dr. Mickelson stated that it is imperative that this group reach conclusion on SAE rep

because this issue cannot be left unresolved.

XXIII. Future Meeting Dates/Dr. Mickelson

The next RAC meeting will be held June 28-30, 2000, at the National Institutes of Health, Building 31C, Conference Room 10, Bethesda, MD.

XXIV. Adjournment/Dr. Mickelson

Dr. Mickelson adjourned the meeting at 3:10 p.m. on March 10, 2000.

[Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, actions are considered final until approved by the NIH Director

Amy P. Patterson, M.D.

Executive Secretary

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

Date: 6/28/2000

Claudia A. Mickelson, Ph.D.

Chair

Recombinant DNA Advisory Committee

National Institutes of Health

Attachment I. Abbreviations and Acronyms

AAV adeno -associated v

AAV-hFIX AAV engineered for expression of human clotting Facto

ADA adenosine deaminas

ADEERS Adverse Event Expedited Reporting Syst

Ad5-CD/ *trep* a replication-competent adenoviral vector

AdSAT adenoviral safety and toxici

AdV-hIL-12 adenoviral vector expressing human IL12

AdV-mIL-12 adenoviral vector expressing murine interleukin-

AE adverse event

ALS amyotrophic lateral scleros

ALT alanine transamin

ARCA attenuated replication-competent adenovir

ASGT American Society of Gene Thera

ASPA aspartoacyl

AST aspartate transamin

BIO Biotechnology Industry Organization

CD Canava's diseas

cDNA complementary D

CNS central nervous system

DHHS Department of Health and Human Services, U.

DSMB data safety and monitoring boa

FDA Food and Drug Administration, U.S.

FIAU 2'-fluoro-1-a-D-arabinofuranosyl-5-iodo-urac

FVIII Factor VI

GTR gene transfer resear

HCV hepatitis C vir

hFVIII human Factor VI

hFIX human Factor

HIV human immunodeficiency virus

HPV human papillomavi

HSV-tk herpes simplex virus thymidine kinase

IBC Institutional Biosafety Committee

IHA intrahepatic ar

IL-12 interleukin-12

IM intramuscular

IND Investigational New Drug Applicati

IRB Institutional Review Boa

IT intratumora

IV intravenous

miniAdFVIII vector minimum adenoviral vector for Factor VI

mRNA messenger RNA

NAA N- acetylaspart

NCI National Cancer Institute

NHF National Hemophilia Foundati

NIH National Institutes of Heal

NIH Guidelines NIH Guidelines for Research Involving Recombinant DNA Molec

NMR nuclear magnetic resonan

NOAEL no observable adverse effect lev

NORD National Organization of Rare Disorde

OBA Office of Biotechnology Activities (formerly ORDA , Office of Recombinant DNA Activit

OPRR Office for Protection from Research Ris

OTC ornithine transcarbamyl

PCR polymerase chain reacti

PEG-ADA polyethylene glycol-conjugated bovine adenosine deaminas

p/kg particles per kilogram

PSA prostate-specific antig

Q&A question and answer

RAC Recombinant DNA Advisory Committee

SAE serious adverse eve

SCCHN squamous cell carcinoma of the head and

SCID severe combined immunodeficien

ATTACHMENT II. COMMITTEE ROSTER

C. Estuardo Aguilar-Cordova, Baylor College of Medici

Dale G. Ando, Cell Genesys , In

Xandra O. Breakefield , Massachusetts General Hosp

Louise T. Chow, University of Alabama, Birmingham

Theodore Friedmann , University of California, San Die

Jon W. Gordon, Mount Sinai School of Medicine

Jay J. Greenblatt , National Cancer Institute, National Institutes of Heal

Eric T. Juengst , Case Western Reserve Universi

Nancy M.P . King, University of North Carolina, Chapel Hi

Sue L. Levi-Pearl, Tourett's Syndrome Association, Inc

Ruth Macklin, Albert Einstein College of Medicine

M. Louise Markert , Duke University Medical Cent

R. Scott McIvor, University of Minnesota

Claudia A. Mickelson, Massachusetts Institute of Technology

Jon A. Wolff, University of Wisconsin Medical School

ATTACHMENT III. ATTENDEES

Bruce Agnew, freelance reporter

W. French Anderson, University of Southern California

Kiyoshi Ando, NIKKEI, Nihon Keizai Shim

Valder Arruda , Children's Hospital, Philadelphia

Lawrence Bachorik , U.S. Food and Drug Administrati

Stephen Bajardi , National Hemophilia Foundation and National Organization of Rare Disorde

Steven Bauer, U.S. Food and Drug Administration

Ann Besignano , Capital Consulting Corporati

Joanne Binkley, U.S. Food and Drug Administration

Philippe C. Bishop, U.S. Food and Drug Administration

Christine Boisclair , Genzyme Corpora

Peter A. Bootsma , Royal Netherlands Embas

David C. Bowen, Office of U.S. Senator Edward M. Kennedy

Nell Boyce, *New Scientist*

Jeffrey Brainard, *The Chronicle of Higher Education*

Stephen R. Brand, CATO Research

Gordon Bray, Baxter

David F. Broad, Cell Genesy

Diane Bromzert , M

Gary Brouwer , Caly

Vicki Brower, *Nature Biotechnology*

Deborah A. Bumbaugh , Novartis Corpora

C. Channing Burke, Introgen Therapeutics,

Jeffrey W. Carey, GenVe

Mary M. Carey, Targeted Genetics

Christine Cassel , Mount Sinai School of Medici

Joy A. Cavagnaro , Access B

Shu-Hsia Chen, Mount Sinai Medical Cent

Yawen L. Chiang, Aventis Pharmaceuti

Amy Chu , Childr's Hospital, Philadelphia

Karen W. Chu , Gen

Shirley M. Clift , Cell Gene

Odile Cohen- Haguenauer , Hopital Saint-Louis (Paris, F

Patrick Collins, National Hemophilia Foundation

Jodie Corngold , Nord

Linda Couto , Avi

Dave Cureton , cancerpage.

Mike Dake , Stanford Universi

Joann Delenick , orthopedic surge's office

Lynley Donovan, Aventis Pharmaceuti

Ronald C. Dorazio , Gene

Cecily Dorough , National Prostatic Cancer Coali

Lyndah Dreiling , Aventis Pharmaceu

Lingxun Duan , GenWay Biotec

Stephen P. Duprey , Aventis Pharmaceuti

Christopher Earl, Perseu

Maureen A. Early, Rhône-Poulenc Rorer Pharmaceuticals In

Steve Eckert, NBC News

Thomas L. Eggerman , U.S. Food and Drug Administrati

Andrew Eiva , Washington Office for Bosn

Traci Eng, Capital Consulting Corporation

Gail L. Estes, Aventis Pharmaceutica

Faye Flam, *The Philadelphia Inquirer*

Maggie Fox, Reuters America Inc.

Susan Frantzbohn , U.S. Food and Drug Administrati

Tim Friend, *USA Today*

George Fulkalf , Thomas Jefferson Universi

Paul Gelsinger , pare

Barak Goodman, WGBH

Angus J. Grant, Aventis Pharmaceutica

Bea Grause , Genzyme Corpora

Dr. John T. Hamm, Norton Healthcare, Inc.

Jan Hardy, U.S. Food and Drug Administration

Peter Hartogs , CNN America, In

Daniel R. Henderson, Calydo

Rob Hendin , CBS Ne

Nancy L. Herring, Transgen

Michael Hershfield , Duke University Medical Cent

Roland Hertzog , Childr's Hospital, Philadelphia

Kathy High, Children 's Hospital, Philadelphia

Vaughn B. Himes, Genov

Bruce A. Hironaka , Cell Gene

Deborah Hursh , U.S. Food and Drug Administrati

Beth Hutchins, Canji , In

Margot Iverson, American Association for the Advancement of Science

Chris Jansen, Thomas Jefferson University

Dorothy Jessop , citiz

Christine- Lise Julou , Rhône-Poulenc Rorer Pharmaceuticals

James Kaiser, U.S. Food and Drug Administration

George F. Kalf , Jefferson Medical Colle

Bhanu Kannan , U.S. Food and Drug Administra

Grace Kao, Valentis , In

Lisa Kaplan, Capital Consulting Corporation

Helene Karlin , Canavan Research

Lindsay Karlin , patie

Roger Karlin , Canavan Research

Aimée L. Kasenga , Office of Inspector General,

Patricia Keegan, U.S. Food and Drug Administration

Mark W. Kieran, Dana-Farber Cancer Institute and Children 's Hospital, Boston

Rachel King, Novartis Corporati

Donald B. Kohn, Children 's Hospital, Los Angeles

Steven A. Kradjian , Vical ,

Tom Kuchanborg , U.S. Health and Human Servic

Gary J. Kurtzman , Gen

LaVonne L. Lang, Parke-Davis Pharmaceutical Resear

Debra R. Lappin , Arthritis Foundati

Paola Leone, Jefferson Medical College

Ruth Ryan Lessard , Introgen Therapeutics,

Jeffrey B. Levine, Healtheon / WebMD Corpora

Augustine Lin, Aventis Pharmaceutica

Stefan D. Loren, Legg Mason Wood Walker, Incorporated

Deborah Lynch, InClon

Russette M. Lyons, Genetic Therapy, In

Lauren Maddox, Genzyme Corporati

Sridhar Mani , Albert Einstein College of Medici

Katie Manno , Childr's Hospital, Philadelphia

Tanya M. Manor, Genzyme Corporati

Eliot Marshall, *Science*

Cardinali Massimo, U.S. Food and Drug Administrati

Jay McCarty, CBS News

Page McCarty, CBS News

J. Alan McClelland, Avige

Scott McFee , Thomas Jefferson Universi

Maritza McIntyre, U.S. Food and Drug Administrati

Stacy M. Meisberger , Lilly Research Laboratori

James A. Merritt, Introgen Therapeutics, In

Dr. Miller, U.S. Food and Drug Administration

Sarah E. Miers , legislative analy

Alan Milstein, Sherman, Silverstein, Kohl, Rose and Podolsk

Surya Mohanty , Aventis Pharmaceu

Tina Moulton, U.S. Food and Drug Administration

Thomas H. Murray, Hastings Center

David Nance, Introgen Therapeutics, In

Deborah Nelson, *The Washington Post*

Laila Olsen, Chandler Chicco Ag

Stuart Orkin , Harvard Medical Scho

Jeffrey Ostrove , Neuro

David Parkinson, Novartis Corporati

Bharti Patel, U.S. Food and Drug Administrati

Suzanne R. Pattee , Cystic Fibrosis Foundati

Phil Pendergast , Ohio State Universi

Kim Penland*FDA Week*

Glenn F. Pierce, Selective Genetics Incorporated

Anne M. Pilaro , U.S. Food and Drug Administrati

Nicola Y. Pinson, Office of Inspector General, DHH

Barry Polenz , Targeted Genetics Corporati

Gerald L. Price, SRA International, Inc.

Andrew Quon , A

Henrik S. Rasmussen, Gen

Paul Recer , Associated Pre

Reginald Rhein*Scrip, World Pharmaceutical News*

Kristin Ritenour , stude

Linda M. Robertson, Roche Global Development

Bob Roehr*Journal of the International Association of Physicians in AIDS Care*

Charles Rogers, patient

Donna Rogers, citizen

Donna Savage, Capital Consulting Corporation

Leonard J. Schiff, Primedic

John Schmitz, citizen

Lisa Seachrist *BioWorld Tod*

Stephanie H. Seiler, Noonan/Russo Communications, Inc.

Nancy Shapiro, Capital Consulting Corporation

Monica Sharma, Biotechnology Industry Organization

Haimi Shifet*The Blue Sheet*

Tomiko Shimada, Ambience Awareness International, In

David G. Shoemaker, CATO Research

Jay P. Siegel, U.S. Food and Drug Administration

Ed Silverman, *The Star-Ledger*

Stephanie L. Simek, U.S. Food and Drug Administration

Barbara Singer, Capital Consulting Corporation

Paul Smyli

Richard O. Snyder, Harvard Medical School and Children 's Hospital, Boston

Robert Sobol , GenStar Therapeu

Alice L. Sofield , Chandler Chicco Agency

Lorna Speid , Valentis ,

Rebecca S. Spieler, *The Blue Sheet*

Jean Starr, Family Help Center

Donna Cay Tharpe , Capital Consulting Corporati

Larry Thompson, U.S. Food and Drug Administration

Michael Touby , Lanier Marketi

Claire Tse , Aventis Pharmaceuti

Ruth S. Turner, Genzyme Corporati

Claire Turney , University of Texas M.D. Anderson Cancer Cent

Steve Usdyn , BioCent

Dominique A. Vacante , BioRelia

Robert W. Veneziale , Schering-Plough Research Institu

Janet Vessotskie , Schering-Plough Research Institu

Nathalie Vincent, Genethon

Samuel C. Wadsworth, Genzyme Corporati

Karen Weiss, U.S. Food and Drug Administration

Rick Weiss, *The Washington Post*

Michael J. Werner, Biotechnology Industry Organization

Chipper Whalen, Capital Consulting Corporation

Carolyn Wilson, U.S. Food and Drug Administration

Deborah R. Wilson, Introgen Therapeutics, In

Antoine Yver , Aventis Pharmaceuti

Robert Zalaznick , New York Hospital and Cornell Medical Cent

David Y. Zhang, Mount Sinai Medical Center

Karen S. Zier , Mount Sinai Medical Cent