RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 13-14, 2005

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

CONTENTS

[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/rac/protocol.pdf>.]

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]

December 13-14, 2005

The Recombinant DNA Advisory Committee (RAC) was convened for its 102nd meeting at 9:00 a.m. on December 13, 2005, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Diane Wara (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. until 5:00 p.m. on December 13 and 8:30 a.m. until 2:45 p.m. on December 14. The following individuals were present for all or part of the meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania Medical Center
Stephen Dewhurst, University of Rochester Medical Center
Howard J. Federoff, University of Rochester
Helen Heslop, Baylor College of Medicine
Terry Kwan, TK Associates
Nicholas Muzyczka, University of Florida
Glen R. Nemerow, The Scripps Research Institute
Steven Piantadosi, Sidney Kimmel Cancer Center
Madison Powers, Georgetown University
Naomi Rosenberg, Tufts University
Nikunj V. Somia, University of Minnesota, Twin Cities
Richard G. Vile, Mayo Clinic College of Medicine
Diane W. Wara, University of California, San Francisco
David J. Weber, The University of North Carolina at Chapel Hill

Office of Biotechnology Activities (OBA) Director/Acting RAC Executive Secretary

Amy P. Patterson, Office of the Director, National Institutes of Health (NIH)

***Ad Hoc* Reviewers/Speakers**

Gilman Grave, National Institute of Child Health and Human Development (NICHD), NIH
Athena S. Papas, Tufts University School of Medicine
Robyn S. Shapiro, Medical College of Wisconsin
Scott E. Strome, University of Maryland School of Medicine

Nonvoting Agency Representatives

Kristina C. Borror, Office for Human Research Protections, U.S. Department of Health and Human Services (DHHS)
Stephanie L. Simek, U.S. Food and Drug Administration (FDA)

NIH Staff Members
Sarah Carr, OD
Liza Dawson, OD
Kelly Fennington, OD
Lorraine Fitzsimmons, OD

[1] The Recombinant DNA Advisory Committee is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Biotechnology Activities should be consulted for NIH policy on specific issues.

Linda Gargiulo, OD
Gabor Illei, National Institute of Dental and Craniofacial Research (NIDCR)
Robert Jambou, OD
Laurie Lewallen, OD
Maureen Montgomery, OD
Marina O'Reilly, OD
Eugene Rosenthal, OD
Thomas Shih, OD
Frosso Voulgaropoulou, National Institute of Allergy and Infectious Diseases
Anthony Voutetukis, NIDCR
Chang Yu Zheng, NIDCR

Others

There were 86 attendees at this 2-day RAC meeting. Attachment I contains lists of RAC members, *ad hoc* reviewers and speakers, and nonvoting agency and liaison representatives. Attachment II contains a list of public attendees. Attachment III is a list of abbreviations and acronyms used in these Minutes.

I. Call to Order and Opening Remarks/Dr. Wara

Dr. Wara, RAC Chair, called the meeting to order at 9:00 a.m. on December 13, 2005. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on November 21, 2005 (70 FR 70082). Issues discussed by the RAC at this meeting included public review and discussion of six protocols, a gene transfer safety assessment board report, and a presentation regarding risk-benefit assessment in early-phase pediatric research.

Dr. O'Reilly reminded all RAC members of the rules of conduct that apply to them as special Federal Government employees.

II. Minutes of the September 21, 2005, RAC Meeting/Drs. Rosenberg and Somia

Dr. Rosenberg noted that the September 2005 RAC minutes contained no errors.

A. Committee Motion 1

It was moved by Dr. Muzyczka and seconded by Dr. Rosenberg that the RAC approve the September 21, 2005, RAC meeting minutes. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Gene Transfer Safety Assessment Board Report/Drs. Albelda, Heslop, Federoff, and Wara

Dr. Heslop reported that 147 protocol amendments had been filed in the past 3 months, of which 37 were for change of site or principal investigator (PI), 2 were protocol design modifications, 46 were annual reports, 14 were protocol status changes, and 7 were responses to the *NIH Guidelines, Appendix M(1)C(1)*. Dr. Heslop briefly summarized two protocols and noted that none warranted public discussion. In Protocol #0108-494, Gene Transfer of the γc cDNA into CD34+ Hematopoietic Cells of Infants or Children with X-linked Severe Combined Immunodeficiency Disease, the RAC received notification from Dr. Kenneth Weinberg at Children's Hospital of Los Angeles that he was planning to offer enrollment to a patient who had not previously had a bone marrow transplant; the protocol allows for enrollment of such individuals if they lack a matched sibling donor and would have a high risk of morbidity and mortality from an alternative donor transplant. The RAC also received notification that a second single participant exemption would not be pursued for Protocol #0312-619, Administration of a Replication-Deficient Adeno-

Associated Virus Gene Transfer Vector Expressing the Human CLN2 cDNA to the Brain of Children with Late Infantile Neuronal Ceroid Lipofuscinosis.

Dr. Albelda reported that 18 protocols had been submitted to the OBA since September 2005, 6 of which were selected for public review at this RAC meeting. Of the 12 protocols not selected for public review, 9 were for cancer, and 1 each was for peripheral arterial disease, autoimmune disease (multiple sclerosis), and infectious disease (acquired immune deficiency syndrome). Three of these 12 protocols employed plasmid vectors, 6 used adenoviral vectors, and 1 each used a lentiviral vector, a herpes viral vector, and a yeast vaccine.

The OBA staff reviewed the adverse events (AEs) reported. Although none were deemed necessary for public discussion, 11 were A (serious) events, 7 of which were unexpected and 4 of which were expected. One protocol was summarized briefly but did not warrant public discussion. In Protocol #0312-619, a research participant with moderate disease had undergone surgery on September 20, 2005, and eight days later, the participant had two seizures, which were controlled by increasing the antiseizure medication.

Dr. Federoff briefly summarized protocol #0502-699, A Pilot Study of Temozolomide and 0^6-Benzylguanine for Treatment of High-Grade Glioma Using Autologous Peripheral Blood Stem Cells Genetically Modified for Chemoprotection. The PI is placing this trial on hold because of preliminary results from nonhuman animal studies that show abnormal hematopoiesis in several mice. A few of the mice have what appears to be a myeloproliferative disease. Further information regarding the presence or absence of the transgene in these animals, analysis of the multiplicity of infection, the full pathology report, and testing for replication competent retrovirus will be provided.

IV. Risk-Benefit Assessment in Early-Phase Pediatric Research

Presenter: Gilman Grave, M.D., NICHD, NIH

Dr. Grave presented a history of the legislative and legal aspects of early-phase pediatric research, noting a pattern of a childhood tragedy followed by a legislative fiat:

- The Pure Food and Drug Act (1906) was enacted in response to children being given heroin, morphine, and chloroform in their patent medicines to keep them quiet and to stop them from coughing.

- The Food, Drug, and Cosmetic Act (1938) was enacted in response to the death of 107 children who were given sulfanilamide laced with diethylene glycol.

- The Nuremberg Code (1947) stated that only people who can give consent—that is, adults—can be subjected to or enrolled in research.

- The Kefauver-Harris Amendments (1962) to the 1938 Act were enacted as a result of the German thalidomide tragedies in the early 1960s.

- The Pediatric Research Equity Act (2003) was passed unanimously by both houses of Congress to give the FDA the authority to require pediatric drug studies of drugs that were used in children but had not been tested in children.

These pieces of legislation mandated that drugs be tested primarily in adults, with results extrapolated to children, which led to the unintended consequence of several generations of children being given drugs that had not been adequately tested in children. Currently, approximately 80 percent of drugs given to children have never been tested in children.

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [NCPHSBBR], 1978), which was mandated in the National Research Act of 1974, had three key principles: "beneficence, justice, and respect for persons." The report stated that finding effective ways of treating childhood diseases and fostering healthy development are benefits that justify including children in clinical trials. The Commission also mentioned protection from harm by admonishing to "first do no harm," "maximize benefits and minimize harms," and, quoting from French physiologist Claude Bernard, "injure no one regardless of benefits to others." Regarding "respect for persons", *The Belmont Report* indicated that individuals with the capacity to consent (age 18 years and older) should be treated autonomously and that anyone younger than 18 years, by definition, has legally diminished autonomy and is therefore entitled to protection, implying an ethical imperative to obtain assent from children and to inform them of possible risks. *The Belmont Report* also discusses the principle of justice; a key implication of this ethical principle is that children should be exposed to the potential benefits of research rather than being treated as "therapeutic orphans."

The *Basic U.S. Department of Health and Human Services Policy for Protection of Human Research Subjects* (45 CFR 46) is the current Federal policy in this area. Title 45 deals with public health, and Part 46 deals with the protection of human subjects; subpart D is drawn directly from the Commission's report *Research Involving Children*. The four categories of admissible research in children contained in this document are minimal risk ("404"), greater than minimal risk but with the prospect of direct benefit ("405"), minor increase over minimal risk ("406"), and not approvable due to no prospect of direct benefit ("407"). Beyond the scope of the four categories is "presents a reasonable opportunity to further understand, prevent, or treat a serious problem," which is the wording of the DHHS Secretarial review appeal portion of this policy. Subsection 407 describes research that an institutional review board (IRB) could not approve as minimal risk, as a minor increase above minimal risk, or for which no direct benefit is obvious. Of the approximately 500,000 protocols involving children in the United States since 1983 when the rules came out, only 16 protocols have been classified as "407," and some of those 16 have been found, after review, to not be classified as "407." The FDA has comparable regulatory provisions for clinical investigations of FDA-regulated products involving children, including an FDA commissioner review process.

Dr. Grave described the interpretations of minimal risk and direct benefit. Minimal risk takes into consideration that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Direct benefit involves the expectation of success being scientifically sound to justify undertaking whatever risk is involved. When the level of risk is greater than minimal, it must be balanced by the compensating benefit. When considering minor increase over minimal risk without direct benefit, the experiences of the participants should be commensurate with expected medical situations and likely to yield generalizable knowledge of importance to the participants' condition. Studies have shown that there can be very disparate interpretations of the risk and benefit considerations. One survey asked pediatric professors, IRB chairs, and other relevant professionals their opinion of the risk to children of various procedures such as sticking a needle in a child's eardrum to drain the fluid, a sexual activity survey, allergy skin testing, and a 10 mL blood draw once a week for 24 weeks. Responses about the level of risk ranged from minimal (classified as "404") to not approvable (classified as "407"), with no consensus in any category.

Dr. Grave noted that researchers and regulators have learned that drug metabolism in children differs from that in adults; drugs such as gabapentin, etodolac, and fluvoxamine were found to be needed in higher doses in children, and yet the perceived wisdom was that children needed lower doses than adults. AEs in children may not always be predicted from the adult experience; propofol was found to have twice the mortality of other comparable drugs in pediatrics, and ribavirin increased suicidal ideation—unusual events that were revealed in children given these drugs but not in adults. Ethical issues require continued careful assessment in pediatric patients, which is being done currently at the National Academy of Sciences' Institute of Medicine, every time an IRB meets, and at the FDA, which has vastly increased its attention to pediatric therapeutics.

A. RAC Discussion

Dr. Shapiro asked for guidance in defining direct benefit, noting the difficulty in predicting it in research. Dr. Grave responded that a reasonable guidance would be a "gut check" about whether a parent is comfortable enrolling her or his child in a particular protocol.

Dr. Wara noted that in her role as an IRB member, she finds it difficult to separate the risk:benefit assessment from an evaluation of the science. Dr. Grave agreed that studies need to be scientifically as well as ethically sound to justify the risk involved.

Dr. Weber asked for some discussion about the role of assent. Dr. Grave explained that the Commissioners believed that it was up to local IRBs to determine whether each individual participant was capable of assent. At the NIH, age 7 years is considered the age of assent, but that age is arbitrary. Assent should be tailored to the individual. In some cases, guidance has stated that an IRB should have a proxy or liaison follow the assent process in individual children, depending on the severity of possible harms that could result from the study.

Dr. Weber wondered how severe a disease needs to be before the parent's consent would override the child's assent. Dr. Grave stated that a number of documents and guidances discuss this issue. If there is no other way the child could get similar therapy and this protocol is the only avenue to improving the child's health but the child declines to participate, the parents can override the child's preference and enroll the child in the study.

Dr. Federoff asked how duration should be considered in assessing risk. Dr. Grave responded that the considerations should be how long the child would be exposed to the risk, and whether any harm can be reversed.

V. Discussion of Human Gene Transfer Protocol #0510-740: A Phase I Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral (AAV) Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium (RPE)

Principal Investigator:	Albert M. Maguire, M.D., Scheie Eye Institute, University of Pennsylvania Health System
Additional Presenters:	Jean Bennett, M.D., Ph.D., University of Pennsylvania; Fraser Wright, The Children's Hospital of Philadelphia; and Chris Rockey, patient advocate
Sponsor:	Katherine A. High, M.D., Howard Hughes Medical Institute
RAC Reviewers:	Dr. Powers, Ms. Shapiro, Dr. Vile, and Dr. Wara

Drs. Albelda and Nemerow recused themselves from reviewing this protocol because of conflicts of interest.

A. Protocol Summary

LCA is a severe, early-onset retinal degeneration, with diagnosis usually made within the first few months of life. LCA is incurable and untreatable, and the significantly impaired vision present at birth progresses to total blindness. This study will focus on the form of LCA caused by mutations in the gene encoding the 65 kDa retinal pigment epithelium -specific protein (RPE65). Clinical diagnosis is made by visual function testing, and molecular testing identifies the causative RPE65 mutations unambiguously.

Progressive cell loss has been demonstrated in individuals with LCA. A study population composed of children with LCA in the 8- to 18-year-old age group is appropriate for assessing toxicity and safety, since patients in this age group show evidence for maintained retinal thickness and cell population. Thus, they possess retinal cells that are viable and amenable to treatment. In contrast, older patients have far fewer cells that could be rescued by treatment.

The vector chosen to deliver the gene is derived from an adenoviral associated virus (AAV), a nonpathogenic, single-stranded deoxyribonucleic acid (DNA) virus that, in the wild, requires helper adenovirus for replication. AAV.RPE65 employs the AAV as a delivery vehicle for the normal human *RPE65* gene.

The study proposed is a Phase I dosing study to assess the safety of an AAV-based gene transfer material containing the human gene encoding RPE65. The primary objective is to determine the safety and tolerability of retinal administration of AAV.RPE65. Secondary objectives include determination of the dose amount of AAV.RPE65 that most effectively restores RPE65 activity as determined by visual function and retinal function tests.

B. Written Reviews by RAC Members

Three RAC members voted for in-depth review and public discussion of this protocol. Key issues included the proposed enrollment of children in a protocol which may pose more than minimal risk for a disorder that is chronic and not life threatening. In addition, a similar study proposed in adults is not yet under way and therefore has not yet yielded clinical data on which to base estimations of the intervention's risk in children.

Noting the Federal standard of allowing children to participate in nonbeneficial research that poses more than minimal risk only when it is likely to yield generalizable knowledge about the child's disorder or condition, Dr. Powers requested that the investigators discuss their understanding of how this standard applies in this study and what guidance has been provided by the relevant IRB. He requested clarification as to whether research in a pediatric population is necessary to obtain information of potentially unique relevance to the patient population not otherwise obtainable by research on adults. He requested additional information about the age selection criteria for this study and details about the administration of the proposed quality-of-life assessment document. Regarding the assent process, Dr. Powers asked whether a written assent document would be used, who would be present or otherwise involved in showing the informational video and obtaining the required assent, and what variations might be present in the risk information disclosed to the participating children compared with the risk information provided to those children's parents.

Ms. Shapiro noted the *NIH Guidelines* direct that for protocols involving children, special attention must be paid to Subpart D which states that for research involving greater than minimal risk but presenting the prospect of direct benefit, the risk must be justified by the anticipated benefit to the subjects. She requested that the investigators expand on their risk-benefit evaluations and discuss justification for the proposed sample size in light of the importance of sample size as a component of minimizing and ensuring reasonableness of risk. Regarding the informed consent process and document, she suggested some wording changes for clarity, including a rewrite of the "Additional Risks," "Will I Have to Pay for Anything?," and "Additional Financial Considerations" sections. Ms. Shapiro had several concerns about the assent process—how the child participant's assent would be obtained, whether obtaining valid assent from all prospective child participants would be possible, whether the permission of both parents would be required, and whether a prospective child participant's dissent would be respected if that child's parents favor participation.

Dr. Vile requested further information concerning the rapid ocular inflammation that occurred in one of the experimental dogs, the integration status of the vector after injection, and the results of studies to detect any autoimmune reactivities, which may arise against the normal form of the protein and lead to long-term toxicities. He asked whether results were available for the continuing studies to examine repeated administration, and whether the investigators have any evidence of chronic immune reactivities against the transgene product in treated dogs. Noting that the LCA gene transfer trial in adults included some preclinical studies with cynomolgus monkeys, Dr. Vile asked whether the data from those studies are relevant and whether they are available to the current study's investigators.

Dr. Wara asked that the investigators present the preclinical toxicity data derived from gene transfer in the mouse and dog models as well as any available data from the nonhuman primate studies performed in

conjunction with the LCA gene transfer trial in adults. Additional requests for data from the preclinical studies included the evidence for the absence of vector spread beyond the retina, the evidence for the absence of vector transmission from mother or father to infant, and the range of antibody titers to AAV and RPE65 following gene transfer. Regarding the clinical trial design, Dr. Wara asked for a discussion of other experiences with subretinal injections in the proposed age group, the anticipated extent of risk in the proposed participant population, how the dose amount was determined, which safety data will be assessed prior to progression to a higher dose, and what time interval would be allowed before dose escalation to assess dose-limiting toxicity (DLT). In reviewing the consent process, Dr. Wara noted that the consent document appears to understate the risk of corneal decompensation and other potential surgical complications. She suggested that the investigators include in the informed consent document information regarding the risk of receiving either too much or too little of the transgene.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

- Dr. Powers asked whether proceeding first in a staged way with further adult studies would provide the investigators with information that might change the risk-benefit profile for child participants.

- Ms. Kwan suggested that the investigators evaluate potential participants in the preteen and early teen years as well as participants' family support systems and the dynamics within the family when selecting a participant.

- Dr. Piantadosi suggested the possibility of a shared data and safety monitoring board (DSMB) for this trial and the parallel adult trial.

- Dr. Dewhurst asked whether older children who are potential participants might have a scarred or damaged retina that would preclude potential benefit from this protocol and if this could be determined.

- Dr. Piantadosi expressed concern regarding whether the design of the study was valid for the stated purposes. The denominator chosen for these cohort sizes of three individuals, although not unusual for Phase I clinical trials, may not be appropriate given the dual goals of safety and tolerability. He suggested adding definitions of "safety" and "tolerability" in the outcomes section of the protocol and discussing how the acquired data will be used to reliably assess the outcomes.

- Dr. Vile asked whether any data exist on injecting dogs at different ages, particularly whether the inflammation associated with that injection is more aggressive in younger dogs or in younger nonhuman primates. He noted that the risk in this protocol is likely to be associated with the intensity of the local reactivity, which might be higher in a younger immune system.

- Dr. Piantadosi asked why the risk-benefit is appropriate for one eye but not for two eyes in a given participant.

D. Investigator Response

Dr. Maguire explained that the age selection criteria for the protocol were determined by the need to collect safety data in the population where efficacy trials will occur in the future. The ability to derive direct benefit from the gene transfer decreases with age due to time-dependent degeneration of the retina. However, subjects less than three years old would be at greater risk of amblyopia, a risk that ceases after six-eight years of age. Therefore, subject of 8-18 years of age would not be at additional risk of vision loss due to surgery-induced amblyopia.

Regarding the risk:benefit analysis, based on the animal study results, the investigators considered that there is a prospect of direct benefit to participants in the study. It will need to be determined by the IRB whether the risks of general anesthesia and the surgical procedure are considered greater than minimal risk.

The sample size is typical of other early phase gene transfer protocols and kept at a minimum to expose fewer participants to risk. Also LCA is a rare disorder limiting the number of participants eligible to enroll.

Vector integration has been studied *in vitro* in RPE cells and to a limited extent *in vivo* and little vector integration was observed. The investigators attributed the stability of the effect to maintenance of vector DNA in episomal form in long-lived target cells that do not divide.

Dr. Maguire explained that autoimmune reactivity to RPE65 had not been detected in the dog studies which spanned two months to 3.5 years, with one dog studied for 5.5 years. Re-administration of the AAV2 vector is also being investigated and had been achieved in retinal cells. There was no evidence of immune filtration in the eyes in those experiments.

A GLP non-human primate study was conducted in cynomologous monkeys; however, the investigators did not have access to the complete data for public presentation. Some of the same investigators participate in the adult and pediatric LCA protocols; however, the protocols had different sponsors. Dr. Vile noted that there should be a greater level of open communication between the studies so that relevant data is shared.

Dr. Maguire explained that the investigators are defining safety in this protocol as a lack of toxicity, and they have defined the DLTs on the basis of the World Health Organization Toxicity Scale for the systemic aspects of abnormalities. They have adapted their ocular toxicity scale from a gene transfer study that is currently in Phase II trials and have expanded on it to look specifically at DLTs with regard to the eye. The absence of DLTs is the unstated definition of safety. Stopping rules will be in place.

Regarding assent, consent would be obtained from both parents prior to beginning the assent process with the child participant. The information disclosed would be appropriate for age and comprehension level and audio recordings would be provided. If the prospective child participant dissents, the child will not be included in the trial.

Vertical transmission of the vector or transgene was tested indirectly in the offspring from dog and mouse models. Animals who had received vector were used for breeding in both models and all of the offspring were affected by the disease.

In response to Dr. Vile's suggestion regarding testing the eyes of younger nonhuman primates, Dr. Bennett responded that, in reviewing the data from these animals at different ages, there does not appear to be any clear-cut evidence of increased inflammation with increased age of treatment.

Dr. Maguire explained that visual function includes a lot of redundancy. In the worst-case scenario of completely lost function in one eye, an individual would not lose 50 percent of visual function because of visual acuity overlap between the two eyes. Because of this overlap, injecting one eye is much less risky than injecting both eyes.

Dr. Maguire stated that potential participants between 16 and 18 years old would have considerable areas of degenerated fused retina that may not be amenable to treatment, but including those older children in this protocol is still more appropriate than using adults, since they are likely to have some patches of retina with some viable cells that would potentially be amenable to gene transfer. A retinal degeneration expert is working with the investigators to determine whether coherence tomography could be used to identify patches of retina with viable cells.

E. Public Comment

Chris and Kelly Rockey, patient advocates and parents of 1-year-old Ty Christopher Rockey, who has LCA, described their son's life and discussed the importance of moving forward with this research.

Betsy and David B. Brint, patient advocates and founders of the Foundation for Retinal Research in 1994, described their 8-year-old son Alan's life and discussed the importance of this research moving forward.

Dr. Borror commented that some of the language in the informed consent document was too complex.

F. Synopsis of RAC Discussion and RAC Recommendations

Regarding the central question about this protocol, namely the risk-benefit assessment for pediatric participants, the RAC identified the following study risks: surgery and general anesthesia; vector distribution beyond the injection site, which occurred in preclinical nonhuman animal models; autoimmune response or inflammation in the treated eye; and diminution of visual function in the treated eye. Taken together, these risks were assessed as constituting "slightly greater" than minimal risk. In terms of potential benefit, the RAC concluded, on the basis of data from the preclinical canine and rodent models, that the protocol presented a prospect of direct benefit to individual participants. Thus, the ratio of risks to potential benefits was considered to be reasonable, and the RAC concluded that conducting the study in pediatric participants was ethically appropriate. The RAC recognizes, however, that its recommendations are advisory and that the investigators' IRB will make the official determination about the risk-benefit assessment as well as about any other human participants concerns in the protocol.

The following additional observations and recommendations were made during the RAC's in-depth review and public discussion:

- A similar protocol is being conducted in adult patients with LCA (Protocol #0410-677, Phase I Trial of Ocular Subretinal Injection of a Recombinant Adeno-Associated Virus [rAAV-RPE65] Gene Vector in Patients with Retinal Disease Due to RPE65 Mutations). The PI of Protocol #0410-677 and the investigators of Protocol #0510-740 are collaborators. Because of the shared concerns about risks in the two trials and the small numbers of participants planned for each trial, communication and data-sharing between the groups are scientific and ethical imperatives. The histopathology data assessing long-term sequelae in nonhuman primates should be available to both groups to inform ongoing risk assessment and dosing for human studies. The investigators are urged to make every effort to collaborate with the investigators of Protocol #0410-677. One way of effecting a closer alignment between the studies would be to establish a common DSMB for both trials.

- The scientific validity of the study design was questioned. Although the protocol's primary objective is to determine the safety and tolerability of retinal administration of AAV.RPE65, the number of participants in each dose cohort is not large enough to allow a definitive determination to be made. Even if no AEs occur within a particular cohort, there still could be as great as a 70 percent probability that an AE would occur in a larger sample of participants. Similarly, it will be difficult to achieve the protocol's secondary objective of determining the dose amount that most effectively restores RPE65 activity, because any estimate of efficacy based on such a small cohort is not likely to be reliable. For example, if an efficacy level of 30 percent were achieved, it could overestimate the level of efficacy that would be observed in a greater number of participants.

- LCA is a progressive degenerative condition, and the condition in pediatric participants is expected to be less advanced than in affected adults. However, given that the pace and extent of disease progression can vary, it is important to screen prospective participants as carefully as possible to characterize the viability of their retinal cells. All assays and screening procedures should be described in the protocol and in the informed consent document, and how the results will be used—for example, as exclusion/inclusion criteria—should be clearly stated.

- Since the normal form of the RPE65 protein could cause an autoimmune reaction and lead to long-term toxicities, participants should be monitored for autoimmune responses through long-term followup studies. Long-term monitoring for autoimmune reactions and toxicities also should be conducted in the preclinical nonhuman animal models.

- It is important to assess the psychological status of children and adolescents with LCA and their ability to understand the protocol, including the uncertainty of any potential benefit. A formal psychological evaluation of prospective participants should be part of the participant selection process.

- The informed consent document should be simplified to enhance its readability.

G. Committee Motion 2

It was moved by Dr. Weber and seconded by Dr. Heslop that the RAC recommendations, summarized orally by Dr. Wara, be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 12 in favor, 0 opposed, 0 abstentions, and 2 recusals.

VI. Discussion of Human Gene Transfer Protocol #0510-732: A Phase I/IIA Dose-Escalation Trial of Intratumoral Injection with Oncolytic Adenovirus Vector INGN 007 (VRX-007) in Patients with Advanced Solid Tumors

Principal Investigator:	John Nemunaitis, M.D., Mary Crowley Medical Research Center
Additional Presenters:	Neal N. Senzer, M.D., Texas Oncology, P.A., and William Wold, Ph.D., St. Louis University School of Medicine
Sponsor:	Introgen Therapeutics, Inc.
RAC Reviewers:	Drs. Albelda, Dewhurst, and Powers

A. Protocol Summary

Adenoviral gene therapy for cancer has been widely investigated using replication-defective and conditionally replicating adenoviral vectors. However, their anti-tumor effects have not yet been optimized in the clinic, a situation likely due to a less-than-complete transduction of tumor cells. To try to circumvent this limitation, the replication-competent vector INGN 007 has been developed. Derived from Ad5, INGN 007 mediates the overexpression of the adenovirus death protein (ADP) that functions in the normal adenovirus life cycle to cause infected cells to lyse and release infectious progeny adenovirus. The overexpression of ADP causes a more efficient lysis of infected cells and more rapid overall life cycle. As a result, INGN 007 spreads from cell to cell more quickly than vectors that express normal levels of ADP, thereby causing a more rapid lysis of cancer cells. While INGN 007 has no genetic features specifically restricting replication to cancer cells, the vector appears to have less effect on normal cells. Ad5 and INGN 007 replication and cell killing are greatly attenuated in quiescent normal cells. Even in proliferating normal cells, INGN 007 replication produces a lower virus yield per cell than in cancer cells. In addition the adenoviral immune evasion genes encoded by the E3 region are deleted in INGN 007, which should make the vector more susceptible to the immune system than Ad5.

INGN 007 demonstrated the ability to kill cancer cells while having comparatively little effect on normal human cells in culture. INGN 007 also has been shown to inhibit tumor growth in nonhuman animal models of cancer, even in models of aggressive tumors. Little or no toxicity was observed in nonhuman animal safety studies of INGN 007 at the dose amounts proposed for this clinical trial.

The main objectives of this research study are to determine the safety and the maximum tolerated dose (MTD) of INGN 007. The secondary goals are to follow the distribution of the drug in the blood and urine after direct injection into a tumor and evaluate any antitumor effects of INGN 007 in advanced solid

tumors. This study is designed for participants with one to three superficial tumors (each of 2 centimeters to 5 centimeters in diameter) that are accessible for direct visual evaluation.

B. Written Reviews by RAC Members

Five RAC members voted for in-depth review and public discussion of this protocol. Key issues included novelty of the vector and absence of targeting components that could prevent unintended viral replication in nontargeted tissues.

Dr. Albelda requested a discussion of the preclinical toxicology testing for replicating adenoviruses, specifically why this testing was conducted in mice in which the vector will not replicate, whether human adenovirus replicates sufficiently well in cotton rat and Syrian hamsters to justify their use as predictive preclinical models, and the general validity of preclinical testing of replicating adenoviral vectors. Dr. Albelda asked the investigators to review the efficacy data for ribavirin and cidofovir, the two antiviral agents proposed for use in case of disseminated adenovirus infection.

Dr. Dewhurst asked whether the *in vitro* replication and spread of INGN 007 had been compared to wild-type adenovirus in cultured normal cells and whether INGN 007 has a selective growth advantage that could lead to increased shedding or transmission to uninfected individuals. He also asked about replication and pathogenicity of INGN 007 within lung tissue and the applicability of the hamster and cotton rat models to study this. He asked whether virus would be isolated from participants who develop respiratory symptoms during the course of the trial. He recommended inclusion in the informed consent document of a mention of the death that resulted from administration of a recombinant adenovirus in 1999

Restricting his review to issues of biomedical ethics, Dr. Powers also requested that the informed consent document include information regarding the prior death of a research participant receiving gene transfer using an adenovirus vector.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

- Dr. Nemerow asked for a discussion of the fact that this vector lacks the E3 region, which may affect immune response in the lung.

- Dr. Piantadosi noted that because the dose escalation terminates at a highest dose which is expected to be safe, a maximum tolerated dose (MTD) is unlikely to be determined by this protocol design. Rather the investigators should define an optimal dose, operationally, clinically, or from a safety point of view, and select a dose range that brackets that optimal dose. Using the MTD terminology could confuse other researchers and prevent the use of higher doses which may be appropriate in other situations such as in combination with radiotherapy.

- Dr. Muzyczka asked why the Ad vaccine was developed for military recruits.

D. Investigator Response

Dr. Wold explained that toxicology studies were performed in mice at the request of the FDA because mice are a more sensitive species for determining maximum tolerated dose. Because mice are not permissive for Ad replication, studies were also conducted in Syrian hamsters and cotton rats, which are more relevant preclinical models because both Ad5 and INGN 007 replicate well in cotton rat and Syrian hamster cancer cell lines and *in vivo*.

INGN 007 has no genetic features designed to restrict replication to tumor cells; however, vector replication in normal cells produces less virus yield per cell that in cancer cell lines. Replication of Ad5 and INGN 007 is greatly attenuated in quiescent normal cells as compared to proliferating cells. Adenoviruses may replicate more efficiently in cancer cells than in normal cells because cancer cells

have a deregulated cell cycle that normal cells do not possess, and the virus needs to deregulate the cell cycle to replicate efficiently. The overexpression of ADP in INGN 007 accelerates the release of progeny virus.

Dr. Wold stated that the overexpression of adenovirus death protein (ADP) by INGN 007 does not increase the yield of virus per cell, but it does speed up the time at which the cells lyse, in part because the vector ADP is synthesized earlier in the late stage of infection than is the ADP protein in wild type virus.

To evaluate vector replication and pathogenicity in the lung, biodistribution studies were conducted in Syrian hamsters. INGN 007 and Ad5 were found to replicate in the lung for one week after intratumoral or intraveneous administration, however no pathological effects were observed.

Regarding the efficacy of ribavirin and cidofovir to treat disseminated Ad infection, preclinical data indicates that both drugs inhibit replication in human cell lines and a rabbit ocular model. Clinical data is limited because such infections are rare, but the investigators did cite reports of some successful use of the drugs in patients.

The investigators did not plan to isolate virus in the event of a respiratory infection in a participant. The participant would be treated with intravenous ribavirin or cidofovir.

Dr. Wold explained that the lack of an E3 region in the virus may be a safety feature since the E3 genes function to prevent the killing of affected cells by cytotoxic T lymphocytes and probably, natural killer cells also. Long term studies would be needed to determine if the E3 deleted vector would be eliminated more efficiently.

Dr. Senzer agreed that the protocol is designed to more likely determine a biologically effective dose than an MTD. In the future, the investigators plan to use the vector in combination with other forms of treatment.

Dr. Wold explained that the vaccine was developed for military recruits to treat acute respiratory disease, which is a significant problem for young soldiers under the stress associated with boot camp. They become susceptible to infections by serotype 4 and serotype 7 in the United States and serotype 14 in Europe.

E. Public Comment

Dr. Borror stated that much of the language in the informed consent document is too complex and should be simplified.

F. Synopsis of RAC Discussion and RAC Recommendations

The RAC noted that the development of a nonhuman animal model applicable to safety studies of replication-competent adenoviral vectors would make an important contribution to the field of human gene transfer research and that the investigators should continue their studies with the model to define the underlying mechanisms that cause differences in tumor cell lysis by the INGN 007 vector compared with the wild-type adenovirus serotype 5. The committee's remaining concern was with the informed consent document, which needs further work to enhance its readability.

G. Committee Motion 3

It was moved by Dr. Heslop and seconded by Dr. Albelda that the RAC recommendations, summarized orally by Dr. Wara, be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VII. Discussion of Human Gene Transfer Protocol #0510-734: An Open-Label, Phase I, Dose-Escalation Study of AD-EGFR-CD533 and Surgery for Patients with Resectable Recurrent High-Grade Glioma

Principal Investigators:	William C. Broaddus, M.D., Ph.D., Virginia Commonwealth University (VCU) Medical Center, and Theodore D. Chung, M.D., Ph.D., VCU Medical Center
Additional Presenters:	Kristoffer Valerie, Ph.D., VCU
RAC Reviewers:	Dr. Federoff, Ms. Kwan, and Dr. Nemerow

A. Protocol Summary

High-grade gliomas are among the most lethal forms of cancer. The current standard treatment of these malignancies includes surgery, radiation therapy, and chemotherapy, but even with such an aggressive approach, the median survival remains about 9 to 12 months.

Epidermal growth factor receptor (EGFR) has been shown to play a role in the development of a number of cancers, including high-grade gliomas. These molecules are normally responsible for growth and differentiation of a number of different cells; in cancer, EGFR may be involved in the uncontrolled growth and spread of malignant cells and has been shown to be critically involved with the development of resistance to radiation therapy. In an effort to limit the effects of EGFR activation in tumor cells, the investigators have developed a genetic approach to inhibiting EGFR activation using a dominant-negative mutant form of EGFR called CD533. Experiments in cell cultures and nonhuman animals have shown that expression of this protein inhibits growth and induces cell death, with and without ionizing radiation (IR).

The purpose of this trial is to establish the safety and tolerability of the adenoviral vector that directs the production of CD533 upon infection of the tumor cells. This virus does not have the ability to divide and produce more virus because of specific deletions in the DNA. The protocol incorporates a direct infusion of viral particles into the tumor utilizing a continuous positive pressure system adapted at the VCU for virus delivery. A catheter will be placed at the time of stereotactic biopsy, and the virus will be infused over a period of 4 hours to 40 hours, depending on the volume of virus infused.

Initially, the protocol will test the effect of increasing the volume of the virus, keeping the actual number of viral particles constant at 10^{11} particle units (pus) to confirm the safety of delivering a relatively small dose of viral particles in progressively larger volumes of infusate. Because this specific virus has not been administered previously to humans, it will be injected directly into the tumor to maximize the potential for safety and efficacy. Once the optimum volume has been determined, the viral dose then will be titrated up to $3x10^{11}$, $1x10^{12}$, $3x10^{12}$, and $1x10^{13}$ pfus. Doses will be escalated among five cohorts using a standard Phase I dose-escalation design, and the planned dose escalation will continue unless severe toxicities warrant halting it. Three days after infusion, the participants will undergo definitive removal of the tumor, which will be assessed for viral distribution, production of the dominant-negative protein, and cell death.

The study is designed to address the safety of the vector and assess whether the continuous positive pressure system will enhance the volume of distribution. Safety assessments, including blood testing, physical examinations, and collection of information about AEs, will be carried out daily following injection of the virus into the tumors. Viral replication, gene expression, and inflammatory cell infiltration in tumors will be assessed by comparing a small piece of tumor tissue obtained before infusion with tumor tissue obtained following the infusion. Tumor shrinkage following infusion and subsequent time to tumor progression will be assessed.

B. Written Reviews by RAC Members

Six RAC members voted for in-depth review and public discussion of this protocol. Key issues included that the vector, which encodes a dominant-negative EGFR, has not been used or evaluated in humans and the method for measuring the proposed dosage.

Dr. Federoff asked whether EGFR-CD533 could trans-heterodimerize and disrupt any of the neural relevant receptor tyrosine kinases. Liver toxicity in the form of hepatic necrosis was observed at the highest dose delivered to the mouse limb and was stated to be 2,000-fold greater than the proposed dose in this clinical trial. Clarification is needed as to the exact relationship between this toxic dose and the proposed clinical trial doses. He requested discussion of the possibility of potential systemic seepage during the 16 hours to 24 hours following catheter placement and the optimal catheter placement in recurrent glioma patients. He asked how long participants will be observed following EGFR-CD533 infusion and prior to craniotomy and tumor resection and about the expected outcomes with regard to different tumor sizes.

Ms. Kwan asked the investigators to include a nonscientific abstract in their written protocol. She asked for a clear explanation of the study question and how the dosing scheme would provide an answer to that question. Regarding the informed consent document, Ms. Kwan suggested that it undergo a thorough review and rewrite due to complex language and avoid the use of such terms as “treatment”, “therapy”, and “medication”. She also noted that the informed consent document did not appear to sufficiently describe the risks involved in the procedure; in particular, given the poor prognosis of individuals in the targeted population, Ms. Kwan suggested that descriptions of risks include a frank discussion of prolonged and/or significant discomfort compared with palliative care.

Dr. Nemerow requested clarification of the proposed vector dose, discussion of whether the proposed dominant-negative acting transgene product could associate with other growth factor receptors or cell-surface signaling proteins, and clarification of the length of time the transgene is expected to be expressed. Noting that the investigators have carried out relatively limited nonhuman animal toxicity studies to date, he asked for further information as to whether the inflammatory responses observed at higher vector doses in the mouse studies might be related to host responses to the vector alone, to the transgene, or to a combination of both. Dr. Nemerow asked the investigators to comment on whether expression of the transgene being limited to a peak of 3 days would be sufficient to inhibit tumor cell growth and viability.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

Dr. Federoff asked about the nature of the inflammatory responses observed in the rat studies. He asked for further characterization of that inflammatory response, the progression of that inflammatory response with regard to the normal brain parenchymal tissue of neuronal/glial cells, and whether there were any functional outcomes associated with those inflammatory responses.

Dr. Nemerow asked whether overexpression of the transgene could have the effect of upregulating ErbB3 in the tumors cells promoting tumor cell escape.

Ms. Kwan suggested including in the informed consent document mention of the extra surgical procedure and associated additional discomfort.

Dr. Piantadosi recommended reviewing the study design and drafting an analytical plan, including a careful consideration of the study’s objectives, what generalizable knowledge might be gained, and how reliable that knowledge is likely to be.

D. Investigator Response

Dr. Broaddus explained that EGFR-CD533 blocks ligand stimulation of EGFR/ErbB1, ErbB2, and ErbB4 but is associated with a compensatory Tyr kinase activity resulting in phosphorylation of ErbB3. The cytoplasmic kinase domain has been deleted from EGFR-CD533 so that it can not interact with adaptor proteins and transmit ligand-stimulated signaling. Through heterodimerization with other ErbB proteins, EGFR-CD533 acts as a decoy. However, the investigators have not investigated whether there is any interaction between EGFR-CD533 and other receptor tyrosine kinases.

Dr. Broaddus explained that, in the proposed setting, there is no known significant dependence on EGFR for normal neuronal cell function.

Regarding the proposed dosing scheme, Dr. Broaddus clarified that their laboratory used a conversion of 1 plaque forming unit equals 1/20 particle units. He also clarified that the proposed doses will be administered independent of the participants' tumor volumes. The range of participants' tumor volumes will be commensurate with the volume of the proposed maximum dose, because the investigators anticipate that participants will have recurrences of tumors from 1.5 centimeters to 3 centimeters in diameter.

The hepatic necrosis was observed following intramuscular injection at a dose 50-160 fold higher that the dose proposed for the human trial. This will be studied further in the planned toxicology studies using GLC vector stocks.

In response to Dr. Federoff's queries, Dr. Broaddus answered that no functional consequences of the toxicities were noted in the rat studies. The inflammatory changes were mostly inflammatory cell infiltrates in the region localized to the catheter site. He noted one instance of what appeared to be a bacterial abscess, which the investigators believe was related to technique and not to the agent or the delivery process.

Dr. Broaddus clarified that the catheter would be placed only after preliminary pathologic reports confirmed the presence of recurrent high grade glioma. Infusion of the vector will occur 16-24 hours after catheter insertion to allow for adequate patient recovery and for sealing of the catheter tract. The catheter system has a positive-closure mechanism integral to the Luer fitting on its proximal end, so that no seepage should occur.

Dr. Broaddus noted that adenoviral vectors have been reported to express genes differently *in vitro* and *in vivo*. Typically expression peaks at 2-3 days *in vitro* and levels off over 7-14 days, however, *in vivo* longer expression has been observed. Based on several studies, expression is expected to be sufficient to inhibit tumor growth and radiosensitize tumor cells *in vitro* and *in vivo*.

In response to Dr. Nemerow's concern about overexpression of Erb-3 and the potential consequences of an escape, Dr. Broaddus explained that Erb-3 is not known to be a major factor in the biology of gliomas. He noted that tumor cell escape as a result of this strategy is a real possibility, as it is for nearly every other tumor treatment strategy. One of the reasons this particular tumor is so malignant is that it is genetically unstable—when it recurs in the same patient, its biology is different. Eventually, the investigators hope to couple this treatment strategy with radiation and perhaps with other strategies to maximize effectiveness.

E. Public Comment

No public comment was offered.

F. Synopsis of RAC Discussion and RAC Recommendations
Dr. Wara summarized the following RAC comments and recommendations:

<u>Scientific/Medical/Study Design Issues</u>

- The balance between risk and anticipated benefit continues to be of concern because it is not clear whether the risks are reasonable in relation to the potential benefits. The possible harms associated with injecting a large volume of vector-filled fluid into the brain are high, but the benefit of the vector administration may be difficult to determine due to removal of residual tumor mass. Brain tissue adjacent to the tumor may be exposed to the vector infusion, which could be beneficial if any remaining malignant cells are thereby destroyed.

- The following additional risks were noted:

  — The transgene product could associate with and inhibit other receptor tyrosine kinases, growth factor receptors, or cell-surface signaling proteins.

  — If the transgene product is active in nonmalignant cells, it may dysregulate normal cell growth.

- To help define and characterize these risks, additional preclinical studies should be conducted, including the following:

  — Determine whether EGFR-CD533 alters cell proliferation or co-localizes with other receptor tyrosine kinases through tissue culture experiments and nonhuman animal model studies of longer duration.

  — Compare the toxicity of the EGFR vector with that of a standard E1-deleted adenoviral vector lacking the transgene.

  — Investigate the possibility that overexpression of the transgene will upregulate Erb-3 in the tumor cells and cause the tumor to grow by examining residual tumor tissue from nonhuman animal models for the presence of the transgene as well as for overexpression of Erb-3.

- As currently designed, it is not clear whether the protocol will produce generalizable results. To enhance the protocol's ability to produce generalizable knowledge, the protocol design should be revised to include an analytical plan that emphasizes biostatistical analysis.

Ethical/Legal/Social Issues

- Only patients who have already agreed to undergo surgery should be recruited.

- The informed consent document should more fully describe the risks associated with the study procedures involving surgery, catheter placement, and vector injection. It also should include a discussion of the discomforts of the study procedures and the impact of these discomforts on palliative care.

G. Committee Motion 4

It was moved by Dr. Heslop and seconded by Dr. Weber that the RAC recommendations, summarized orally by Dr. Wara, be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VIII. Day One Adjournment

Dr. Wara adjourned Day One of the December 2005 RAC meeting at 5:00 p.m. on December 13, 2005.

IX. Day Two Opening

Dr. Wara opened Day Two of the December 2005 RAC meeting at 8:30 a.m. on December 14, 2005.

X. Discussion of Human Gene Transfer Protocol #0510-739: Transduction of the Upper Airway Epithelium in Humans with Cystic Fibrosis (CF) by an AAV6 Vector that Encodes Human Placental Alkaline Phosphatase (AP)

Principal Investigator:	Moira L. Aitken, M.D., University of Washington
Sponsor:	Dusty Miller, Ph.D., Fred Hutchinson Cancer Research Center
RAC Reviewers:	Dr. Dewhurst, Dr. Heslop, and Ms. Kwan

A. Protocol Summary

CF is a genetic disorder that results in changes in a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). This change in the CFTR affects how salt and water move in and out of the cells in the body, causing an imbalance. As a result, thick mucus develops in the body and can cause many problems, including infections in the lungs and nasal sinuses and blockage of the pancreas and intestines. Treatments for these problems have been beneficial to patients with CF but have not corrected the CFTR defect. Gene transfer aims to correct the CFTR defect by placing a functional CFTR gene inside of the cells.

As a step in the development of a new CFTR vector system for CF, this proposed study will use a marker gene instead of the *CFTR* gene. The marker gene, human placental AP, will be delivered with a specific adeno-associated virus vector (AAV6) into the nose of healthy adult participants. AP expression can be measured by a histochemical assay as a measure of vector transduction. Because AP is a normal human protein, it should not elicit immune responses.

The study is part of a larger plan to evaluate the transduction rates of AAV vectors made from different capsid proteins in airway epithelium of CF subjects to determine if any promote transduction rates that might be suitable for CF treatment. The proposed vector (AAV6-AP) carries a genome derived from AAV2, but the capsid proteins, the primary determinants of transduction efficiency, are from AAV6. In mouse and rat airway and cultured human cells, other AAV6 vectors mediated higher transduction rates than did AAV2 vectors. A safety study in rates of the AAV6 vector found no toxic effects of the vector at doses above that proposed for administration to humans.

The purpose of the proposed study is to determine whether the AAV6 vector can transfer and express AP in the cells that line the inside of the nose in humans with CF. The results will be used to plan future studies with the *CFTR* gene. Participants enrolled in this study will not benefit from being part of this study; however, in the future, it is possible that CF patients will benefit from the knowledge gained about the possibilities for gene transfer using an altered virus to correct the CFTR defect.

B. Written Reviews by RAC Members

Six RAC members voted for in-depth review and public discussion of this protocol. Key issues included the novel vector system (AAV6 with AP), which has never before been used in the human airway, and the limited availability of preclinical data on which to assess the vector system's safety.

Dr. Dewhurst asked whether the investigators have tested for the possibility that intranasal administration of AAV6 vectors in experimental animals results in transduction of brain neurons, including cells within the olfactory bulb and whether the increased transduction efficiency of AAV6 over AAV2, seen in the lung airway epithelial cells of mice, extends to nasal epithelial tissue. He requested further information regarding the AAV6 receptor and/or its tissue distribution and the decision to focus exclusively on the nasal route of delivery in light of the possibility that both efficacy and safety issues in the upper airways may not be predictive of those issues in the lower airways. He asked whether a future trial would focus on a direct comparison of the AAV2 vs. AAV6 vectors.

Dr. Heslop requested a rationale for the investigators' choice of sample size, and study design. She asked for any additional data on biodistribution after intranasal administration of AAV6 vectors in nonhuman animal models, and preclinical data to suggest that the results obtained with intranasal delivery could be extrapolated for future studies targeting the lower airways. She also asked the investigators to provide additional detail about how the outcome of this proposed study would be used to guide future investigations.

Ms. Kwan asked the investigators to share their thinking in selecting the construct and the study design, specifically regarding how the proposed protocol fits into the longer term research model, what the next research steps would be if the investigators' most optimistic expectations are met, and the risks participants would face in light of this protocol's lack of therapeutic benefits. She also requested further clarification in the informed consent document of the possibility that participation in this study could result in participants developing AAV antibodies that might prevent their being able to avail themselves of participating in actual treatments developed using AAV vector-based gene transfer.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

- Dr. Dewhurst requested discussion of the risk that participants might develop an immune response to AAV6 precluding re-administration of an AAV6 vector. As a consequence, if the vectors proved efficacious in future trials, individuals who have been exposed to the AAV vector may find themselves at a disadvantage with respect to potential therapies.

- Dr. Scott E. Strome, University of Maryland, explained that nasal symptoms are one of the most devastating effects of CF, are often the most difficult symptoms to control, and often are directly related to the lung disease. Ameliorating CF patients' nasal symptomatology could potentially help the lung disease, for example, through better irrigation or better exposure. He encouraged RAC members to consider nasal dosing, as proposed in this protocol, not just as a surrogate marker but as a target end point. Dr. Albelda agreed, stating that the nasal epithelium is an appropriate target and useful surrogate for the lung, which would likely not be able to be infected with the vector if the nasal epithelium could not be infected successfully.

- Dr. Piantadosi questioned some of the statistical inferences that are possible with the small number of participants proposed.

- Dr. Albelda suggested that the investigators should discuss using "normal" individuals rather than CF patients as research participants for this protocol. He noted that this trial is expected to be safe as AAV has been administered to hundreds of participants, many in the nose. Therefore, this trial represents a risk low enough that "normal" volunteers would be a reasonable participant population. While gene transfer in the lung would be very different between CF patients and normal volunteers, CF nasal epithelium does not differ considerably from normal epithelium.

- Dr. Wara noted that the RAC had reviewed a previous protocol (0201-514) involving transduction of the upper and lower airway epithelium in healthy subjects by an AAV2-AP vector. At the time of this review, some of the RAC members expressed concern about the risk of bronchoscopy to healthy participants.

- Dr. Piantadosi offered a possible compromise on the issue of enrolling CF patients vs. non-CF individuals. The need to collect more information about safety might lead the investigators to include both; some safety information could be gathered in "normal" participants, and a small cohort of CF patients could be treated as well, to satisfy the concerns about targeting and potential differences.

- Dr. Piantadosi expressed significant general concern about the Phase I trial design. He noted that the off-the-shelf, Phase I trial design was not intended to answer basic safety questions similar to those under examination by this proposed protocol. With only eight participants, AEs and transduction rate data would not be statistically significant to draw meaningful conclusions about the safety or effectiveness of the vector.

- Noting an evolving role for the RAC, Ms. Kwan requested that the RAC begin to develop study design models that would summarize the statistics and the ethics in a guidance document similar to the RAC's informed consent guidance. She urged that a RAC working group on study design be re-constituted and staffed.

D. Investigator Response

Dr. Miller explained that the brain of one rat was studied for possible transduction of brain neurons, but no AP expressing cells were found including in the olfactory regions. In humans, the vector will be administered in the inferior turbinate, an area that does not contain olfactory neurons.

The receptor for AAV6 has not been determined yet; however, it is known that AAV6 uses a different receptor than does AAV5 and AAV2.

While there wasn't sufficient preclinical data to allow for correlation of transduction levels in nasal and lower airway epithelium, studies did detect higher levels of transduction by the AAV6 vector in both locations in mice and rats. The investigators planned to compare the transduction results in the AAV6 trial to a separate trial using AAV2 vectors, which the RAC had reviewed previously (protocol 0201-514). The nasal epithelium was chosen for study because using the lower airways would be significantly more invasive, the tissue is more difficult to sample, and it is more difficult to quantitate what has been transduced. In addition, CF patient-participants would be put at significant risk for bacterial infection if the lower airways were the target tissue in this protocol.

Dr. Miller stated that part of the reason for not immediately using the therapeutic gene is the CFTR transgene is too large for use in an AAV vector. The investigators are developing higher capacity vectors through strategies using dual vectors and *in vivo* homologous recombination.

Vector re-administration had been studied in mice using vectors with different markers. While AAV2 vectors induced a strong immune response preventing transduction upon a second administration, the immune response to AAV6 wasn't completely protective against re-administration as about 50% transduction was achieved.

Regarding the discussion about whether to use CF patients or non-CF individuals, Dr. Miller explained that the use of CF participants would assure that the intended target epithelium was being studied. However, enrollment of "normal" participants would allow faster participant accrual and CF patients would not be potentially immunized. He noted that the human biology and the receptors would not be that different between the two groups.

E. Public Comment

There were no public comments.

F. Synopsis of RAC Discussion and RAC Recommendations

<u>Scientific/Medical/Study Design Issues</u>

- The RAC noted that two features of this protocol are relatively unusual at this stage in the field of gene transfer research:

— The study's purpose is to assess the vector's transduction rate and immunity. As such, the gene being transferred—a human placental AP gene—is not intended to have any therapeutic effect and is being used as a marker of vector transduction.

— Although the ultimate goal is to develop a gene transfer product that would target the lower airways of CF patients, this protocol uses the nasal epithelium as a surrogate target. The clinical data gathered through this protocol are intended to advance the investigators' longer range goal of developing an optimal vector to use in a treatment trial.

- The proposed protocol design raises two major concerns:

— The proposed study cohort is too small. AEs and transduction rate data from only eight participants will not be sufficiently statistically significant to allow meaningful conclusions to be drawn about the safety or effectiveness of the vector. The RAC suggests amending the protocol to include three more participants in the highest dose cohort if gene expression does not occur in at least two participants in the initial cohort.

— The study population—adults with CF—is a concern for scientific and ethical reasons, and it may be more appropriate to first study the vector in healthy, non-CF volunteers. Therapeutic misconception would not be an issue for healthy volunteers. In addition, CF patients who participate in this protocol may not be eligible to enroll in subsequent treatment trials because of immune response to the vector. It may be preferable to enroll healthy volunteers first and then progress to adults with CF if the vector proves effective in the nasal epithelium.

Ethical/Legal/Social Issues

- The informed consent document should be revised as follows:

  — The investigators should add a discussion of their long-range goals and the role the current protocol plays in that long-term strategy.

  — The investigators must thoroughly explain the fact that participants may not be eligible for future treatment studies.

G. Committee Motion 5

It was moved by Dr. Powers and seconded by Dr. Dewhurst that the RAC recommendations, summarized orally by Dr. Wara, be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 13 in favor, 0 opposed, 0 abstentions, and 0 recusals.

XI. Discussion of Human Gene Transfer Protocol #0509-727: Clinical Translation of a Mammaglobin-A DNA Vaccine for Breast Cancer Prevention and Therapy

Principal Investigator:	William E. Gillanders, M.D., Washington University School of Medicine
Sponsor:	Siteman Cancer Center/Barnes-Jewish Hospital
RAC Reviewers:	Drs. Piantadosi, Powers, and Vile

A. Protocol Summary

This proposed Phase I clinical trial will evaluate the safety and feasibility and determine the biologically effective dose of a mammaglobin-A DNA vaccine. The primary objective is to demonstrate the safety and feasibility of the DNA vaccine; secondary objectives are to evaluate the CD4, CD8, and CD4+ regulatory T-cell immune responses to the DNA vaccine. Postmenopausal women with node-positive stage IIA, IIB, IIIA, and IIIB breast cancers would be eligible for participation in this trial. At the time of enrollment,

participants will have completed standard breast cancer therapy, including surgery, chemotherapy, and radiotherapy as appropriate, and will be clinically free of disease.

Participants will be vaccinated with mammaglobin-A DNA, a novel breast cancer-associated antigen, delivered intramuscularly at six different dose levels every 3 weeks for five injections. A total of at least 18 participants will be enrolled. Participants' peripheral blood mononuclear cells will be collected before and after vaccination to measure the T-cell responses induced by DNA vaccination. Specifically, enzyme-linked immunospot assays, intracellular cytokine expression analyses using multiparameter flow cytometry, and peptide tetramer analyses will be used to assess the antigen-specific T-cell response to the mammaglobin-A DNA vaccine. The primary time points for these measurements will be pretreatment and 3 weeks following completion of the five planned injections.

On the basis of the results of this clinical trial, the investigators expect to be able to document the safety and immunogenicity of the mammaglobin-A DNA vaccine. Equipped with these results, they then will be able to design vaccination strategies targeting this novel breast cancer-associated antigen for breast cancer prevention and therapy.

B. Written Reviews by RAC Members

Four RAC members voted to for in-depth review and public discussion of this protocol. Key issues included the potential for development of autoimmunity in participants and the study of a novel transgene product that has never been used in a human gene transfer clinical trial.

Noting that the study design appeared to be based on the type of design used to assess the relationship between dose and safety for cytotoxic drugs, Dr. Piantadosi questioned whether the determination of MTD was appropriate for a DNA vaccine study since significant toxicity had not be reported in other DNA vaccine clinical trials. He suggested that it may be preferable to design a strategy to estimate the optimal dose. There may be some relevant questions regarding the relationship between dose and safety for mammaglobin-A DNA vaccine which could be addressed; however, this might require larger cohort sizes. He also noted that the reading level of the informed consent document may be too high and there was an inconsistency between the consent information regarding pregnancy precautions and the protocol stating only postmenopausal women as eligible.

Dr. Powers focused his review of this protocol on issues of biomedical ethics, especially whether other theoretical risks exist that should be described, based on experience with nonhuman animal models or on other grounds.

Dr. Vile raised a concern in his written review about the potential autoimmune consequences of a successful antimammaglobin vaccination, even though the evidence is strong that the protein is predominantly tumor associated. He asked if animal models to study autoimmunity existed and what type of autoimmune response would be expected in breast tissue. He asked for data showing that the protein or the DNA vaccine has been used with potent immune adjuvants in a nonhuman animal model in which true reactivity to the protein could be raised and where autoimmune reactivities would be observed.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

- Dr. Albelda noted that the way to improve small Phase I trials is to enroll more participants, which significantly increases the trial's statistical power. However, practical problems abound; for example, each participant's care and data analysis increases costs, recruitment is difficult, and time is limited. Researchers face the dilemma of wanting to use as few participants as possible, especially at the doses likely to be ineffective and safe, vs. having enough statistical power to draw meaningful conclusions from those small numbers.

- Dr. Piantadosi acknowledged the dilemma and the scarcity of participants; however, he stressed that it is necessary to ask the proper study questions rather than questions that permit smaller sample size.

- Dr. Strome asked whether the investigators plan to look for tolerance or a negative T-cell response. He noted the equal, if not greater, chance of inducing tolerance compared with inducing antitumor immunity.

- Dr. Strome suggested that the investigators pick one marker for this trial and look at total cellular response to that marker. By looking at multiple markers in a clinical patient population, it is likely to be difficult, if not impossible, to determine toxicity and the appropriate criteria for dose escalation.

- Dr. Albelda recommended that for the stage IV breast cancer participants, controlled vaccinations with influenza, cytomegalovirus, or candida be used first to confirm that participants are able to generate an immune response.

- Ms. Kwan noted that in previous meetings, the RAC had often discussed the inappropriate use of the three-cohort cytotoxic cancer treatment model as the most common trial design for human gene transfer protocols. The role of the RAC is not to approve or disapprove of particular models but to assist the investigators in raising appropriate questions that can be answered during the study.

D. Investigator Response

Dr. Gillanders agreed that the study design had been influenced by phase I oncology studies. The revised protocol clarified the study objectives, the optimal dose and that the MTD would only be determined if it fell within the range of doses under study. However, the investigators believed that a dose escalation design was appropriate because this will be the first use of mammoglobin-A in humans, thus little is know about toxicity.

In the revised protocol, both pre- and postmenopausal women are eligible for enrollment.

Regarding the potential for autoimmunity, the investigators believed that would be limited because mammaglobin-A expression is restricted to breast epithelium and greatly overexpressed in breast cancer cells. Autoimmunity could not be assessed in animal models because no animal homologs of mammaglobin-A have been identified. Because the risk could not be excluded, the protocol had been modified to limit enrollment to participants with stage IV breast cancer.

Dr. Gillanders reported that he had conducted an extensive literature search to address the issue of possible autoimmune reactivity against normal breast tissue and did not find any well-defined natural autoimmune diseases of the breast. He explained that a significant autoimmune reaction involving the normal breast epithelium likely would result in a swelling of the breast, pain in the breast, and destruction of the ability to produce milk. The clinical symptoms would be obvious, could be confirmed with a relatively minimally invasive procedure such as a core biopsy of the breast, and would be easy to treat.

Dr. Gillanders discussed integrating an adjuvant into this trial, an issue that the investigators may revisit in the future now that they have decided to conduct the initial study in stage IV breast cancer patients. However, after considering adding an adjuvant, they chose not to do so because they believe that their ability to document the safety of mammaglobin DNA vaccine might be confounded.

Dr. Gillanders explained that, as the protocol currently stands, there is no formal plan to assess tolerance on a real-time basis. They do propose to measure regulatory T cells and the frequency of regulatory T cells, which may be one of the mechanisms by which tolerance is induced.

E. Public Comment

Dr. Borror commented that the language in the informed consent document is complex and probably would not be understood by most participants. She also noted that the use of the terms "vaccination" and "immunization" might imply effectiveness, so the phrases "experimental vaccination," "experimental immunization," or "DNA injection" should be substituted.

F. Synopsis of RAC Discussion and RAC Recommendations

Scientific/Medical/Study Design Issues

- Although the investigators made an effort to address some of the concerns identified by the RAC during its review (e.g., by modifying the enrollment criteria to limit participants to patients who had been diagnosed with stage IV breast cancer), the RAC remains concerned about the safety of the gene transfer product as follows:

  — Mammaglobin-A, the molecule being used as a therapeutic vaccine, is a tumor antigen; that is, its expression has been correlated with the onset or presence of a particular type of tumor. It is expressed at low levels in normal breast tissue, but its function at those levels and in that setting has not been defined.

  — Even though there are no currently defined autoimmune disorders of the breast, an autoimmune response is a possibility if the vaccine has an effect. The investigative plan to assess the likelihood of an autoimmune response in a future transgenic mouse model is important and could help assess those risks as well as the consequences of ectopic expression.

  — Since it is also possible that the vaccine could induce tolerance rather than a therapeutic immune response, this risk also should be assessed during the study.

- Because patients with stage IV disease may have weakened immune systems, the investigators should review the literature to determine how patients with stage IV disease respond to influenza or other vaccines.

- Although the protocol's stated objectives are to demonstrate the safety and feasibility of the vaccine and to determine the biologically effective dose of the vaccine by evaluating the immune responses to it, the study does not appear to be designed to achieve these goals. The investigators should reevaluate the study design.

Ethical/Legal/Social Issues

- Although the risk of an autoimmune reaction cannot be quantified, it should be mentioned and discussed in the informed consent document.

- In the informed consent document, terms other than "vaccination" and "immunization," both of which may suggest efficacy, should be used in discussing the administration of the DNA product.

- The informed consent document should be simplified to enhance its readability.

G. Committee Motion 6

It was moved by Dr. Federoff and seconded by Dr. Weber that the RAC recommendations, summarized by Dr. Wara, be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 13 in favor, 1 opposed, 0 abstentions, and 0 recusals.

XII. Discussion of Human Gene Transfer Protocol #0510-731: Open-Label, Dose-Escalation Study Evaluating the Safety of a Single Administration of an Adenoviral Vector Encoding

Human Aquaporin-1 to One Parotid Salivary Gland in Individuals with Irradiation-Induced Parotid Salivary Hypofunction

Principal Investigator:	Bruce J. Baum, D.M.D., Ph.D., NIDCR, NIH
RAC Reviewers:	Dr. Federoff, Ms. Kwan, and Dr. Muzyczka
Ad Hoc Reviewers:	Athena S. Papas, D.M.D., Ph.D., Tufts University, and Scott E. Strome, M.D., University of Maryland

A. Protocol Summary

Head and neck cancers affect ~ 500,000 people each year worldwide. Treatment of most head and neck cancer patients typically includes ionizing radiation (IR), which severely and permanently damages their salivary glands and results in little to no saliva production. The lack of saliva leads to problems including trouble swallowing, frequent oral infections, and considerable discomfort. There is no conventional treatment available to correct this condition.

The investigators have been developing a recombinant serotype 5 adenovirus (rAd5) vector based on the hypothesis that a replication-deficient rAd5 vector is capable of safely transferring the human aquaporin-1 (hAQP1) complementary DNA to the parotid glands of adults with IR-induced salivary hypofunction, resulting in a transiently elevated salivary output. Salivary glands have proven to be valuable gene transfer targets in numerous preclinical nonhuman animal model studies. The archetypal water channel hAQP1 is a plasma membrane protein that facilitates water movement across lipid bilayers. Rat and minipig studies have shown that the AdhAQP1 strategy for restoring salivary flow to IR-damaged salivary glands is effective, and studies in rats, nonhuman primates, and minipigs have shown that AdhAQP1 and similar rAd5 vectors are without significant untoward effects after salivary gland delivery.

The purpose of this clinical protocol is to test the safety of AdhAQP1, with some measures of efficacy, in adult participants with established IR-induced parotid gland hypofunction. The targeted tissue site for the AdhAQP1 vector in the proposed study is a single parotid gland. In this Phase I study, safety will be evaluated using conventional clinical and immunological parameters. The primary outcome measure for biological efficacy will be parotid gland salivary output.

B. Written Reviews by RAC Members

Nine RAC members voted for in-depth review and public discussion of this protocol. Key issues included the novelty of the transgene and the tissue target, the non-life-threatening chronic nature of the disorder, and concerns about the adenovirus vector.

Dr. Federoff asked whether the analysis of the nonhuman primate studies indicates which cell types were transduced, the transduction efficiency, and whether extensive fibrosis was observed that might limit access of vector to candidate target cells. Regarding the mini-pig studies, he asked whether the magnitude of saliva formation increase portends improvement in overall clinical status when extrapolated to humans and why the effect was more transient than would be expected due to promoter silencing.

Ms. Kwan focused her review on the need to provide a clear explanation of this protocol. She noted that the language in the informed consent document is complex and should be simplified. Noting that the best-case outcome of this clinical trial would be only temporary, Ms. Kwan asked the investigators to include an explanation of how and in what manner a positive outcome in this study would lead to a next step in ameliorating the chronic condition on a permanent basis.

Dr. Muzyczka suggested using a vector that would be expected to provide more long-term expression, since this chronic problem will be studied in individuals who have survived cancer treatment for 5 years or more. He asked whether the investigators have experience with long-term expression of aquaporin in a nonhuman animal model; if so, Dr. Muzyczka asked to see the data about adverse effects specific to the transgene. Noting that the most troubling data came from the nonhuman primate study, he asked the investigators to summarize what they know about the local inflammatory effects seen following vector

instillation and to comment on what might have happened to produce failure using the high-dose adenoviral vector.

Dr. Papas asked whether the biopsy would attempt to take both acinar and ductal cells and suggested expansion of the exclusion criteria to include autoimmune disease patients who may have salivary hypofunction and patients who smoke. In addition, she suggested that each participant's alcohol usage should be monitored during the study period.

Dr. Strome expressed concern about the extensive manipulation of the parotid duct and the impact this might have on patient care and study outcome. Given that the drug would be administered using an intraductal route, he recommended that the informed consent document be modified to include the relevant risks and that the exclusion criteria be expanded to include individuals whose ducts are not clinically accessible, who have a distal stenosis that would impede drug entry, and who require a general anesthetic for sialoendoscopy. Dr. Strome requested comment from the investigators regarding their choice, for the site of gene delivery, of the parotid ductal system rather than the submandibular ductal system. He suggested limiting the Phase I study to individuals treated for carcinoma in a specific anatomic location (e.g., the oropharynx) and defining a dose range delivered to the parotid as an inclusion criterion.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised:

- Given the duration of expression that is likely to be mediated by this adenoviral vector and given the chronicity of the requirement to establish water flow, Dr. Federoff asked the investigators to discuss how they determined that this vector is the appropriate gene transfer reagent for this patient population.

- Dr. Somia asked about the life expectancy of these patients.

D. Investigator Response

Dr. Baum explained that in the non-human primate studies both acinar and duct cells were transduced but at levels lower than observed in the rat studies. While fibrosis was not observed in any of the animal models, it is possible in the participants who received radiation more than five years previously, thus the participants would be screened by sialogram to exclude individuals with extensive fibrosis.

Dr. Baum described the minipig study as an appropriate model study for what the investigators expect to occur in humans. No steroids were given to the minipigs. The caveat is that the minipigs were irradiated only 16 weeks before they were evaluated, so fibrosis and extended ductal obstruction were different from what is expected in humans. As in the minipigs, the investigators expect to see peak flow in the research participants at day 2 or day 3 followed by a decline due to the immune response to the vector.

Dr. Baum described a result from the preclinical studies that warranted monitoring in the human trial. Female nonhuman animals that received the vector showed a 10 percent decrease in body weight from about day 22 on. Food consumption data roughly correlated with that decrease in body weight. In addition, there was a statistically significant increase in female rats' white blood cell counts up to 10 weeks to 14 weeks after vector administration. Although that increase was statistically significant, the white cell values remained within the normal range for that species of rat. All three observations—body weight, food consumption, and white blood cell count increase relatively late after vector delivery—will be monitored in human females enrolled in this clinical trial.

Regarding the comparison of preclinical and clinical populations, Dr. Baum explained that rats, mice, minipigs, nonhuman primates, and human glands all have the same general structure. The way the glands operate is generally the same. The acinar cells produce a primary isotonic secretion, the ducts resorb sodium chloride, and the salivary glands secrete potassium bicarbonate.

Dr. Baum stated that an adenoviral vector was chosen for several reasons. At the proposed doses (up to $1x10^{11}$), there have been no associated severe adverse effects related to the vector. The investigators therefore hypothesized that this vector would be safe for delivering the proposed gene. The human protocol will test the physiology of the duct cells to determine whether it is akin to duct cell physiology in minipigs and rats; a positive increase in salivary flow will indicate that the general hypothesis holds true. The next step would be to use an AAV2 derived vector to achieve longer effects. When an AAV2 vector is administered to a mouse salivary gland, the vector remains there at reasonable levels and is completely functional for as long as the mouse is alive; mice have expressed transgenes for up to 2 years at the same level as those transgenes measured at 12 weeks after administration. In noting the investigators' conservative approach, Dr. Baum stated that, if this study shows a positive result, then the investigators will have to repeat the nonhuman animal model study in minipigs and toxicology studies in rats with AAV vector.

In response to Dr. Somia's question, Dr. Baum stated that all of the participants in this trial already will have survived 5 years and that their life expectancy is reasonable given the other conditions from which they suffer, such as chronic alcoholism and smoking.

The investigators agreed with the suggestion to exclude smokers and autoimmune patients that may have hyposalivary function but monitoring of alcohol consumption by participants would be difficult. The informed consent document would be modified to include a statement that participants should not consume more than one alcoholic beverage/day during the study.

E. Public Comment

Dr. Borror suggested that the following statement in Section 5.9 of the informed consent document is not helpful and should be deleted: "The risks of the adenovirus vector itself at the dosages to be administered are more accurately described as possible risks." She noted that all risks in a clinical trial are "possible risks" and that risk is a potential for harm to occur.

F. Synopsis of RAC Discussion and RAC Recommendations

Scientific/Medical/Study Design Issues

- It is possible that the inflammatory effects of the study agent and the manipulation of the parotid duct during administration of the agent could confound the interpretation of the data on salivary flow and efficacy. A stent is recommended if obstruction of the duct is observed.

- Preclinical studies suggest that the study agent may cause differential effects in men and women. At 10 weeks to 14 weeks after study agent administration, the amount of inflammation seen in female rats was greater than in male rats. Female rats also consumed less food and lost more weight than male rats, regardless of dose. The investigators should be particularly attentive to the possibility that such differential effects might also occur in human research participants. In addition, the investigators should confer with their IRB about whether these preclinical data warrant discussion in the informed consent document.

Ethical/Legal/Social Issues

- The investigators should simplify the informed consent document.

- The investigators should delete statements about the potential benefits of participating in the study, and given the transient effects of transgene expression, the informed consent document should state that there are no direct benefits to be derived from study participation. For further information, the investigators should refer to the *NIH Guidance on Informed Consent in Gene Transfer Research*, which is available on the OBA Web site at <http://www4.od.nih.gov/oba/rac/ic/>.

G. Committee Motion 7

It was moved by Dr. Muzyczka and seconded by Dr. Rosenberg that the RAC recommendations, summarized orally by Dr. Wara, be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

XIII. Closing Remarks and Adjournment/Dr. Wara

Dr. Wara stated that a clinical trials design working group, as a subset of the RAC, will be re-convened. She expressed her hope that RAC members who actively discussed the various trial design issues at this December 2005 RAC meeting would participate actively in the working group.

Dr. Wara thanked the participants and adjourned the meeting at 2:45 p.m. on December 14, 2005.

[Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, actions are not considered final until approved by the NIH Director.]

_____
Amy P. Patterson, M.D.
Acting RAC Executive Secretary/OBA Director

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

These minutes will be formally considered by the RAC at a subsequent meeting; any corrections or notations will be incorporated in the minutes after that meeting.

Date: _____

_____
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Attachment I
Recombinant DNA Advisory Committee Roster

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Attachment II
Public Attendees

Moira L. Aitken, University of Washington
Jane Atkinson, NIDCR
Bruce J. Baum, NIDCR
Jean Bennett, University of Pennsylvania
Reed Brady, MedImmune Oncology, Inc.
Betsy Brint, Foundation for Retinal Research
David B. Brint, Foundation for Retinal Research
William Broaddus, Virginia Commonwealth University
Patrick J. Burke, Amarex Clinical Research
Andrew Byrnes, FDA
Theresa Chen, FDA
John A. Chiorini, NIDCR
Theodore D. Chung, Virginia Commonwealth University
Jacqueline A. Corrigan-Curay, U.S. Department of Veterans Affairs
Ana Cotrim, NIDCR
Margaret Crowley, Eberlin Reporting Service
Martha French, Introgen Therapeutics, Inc.
Joyce Frey, Pharma Net
Denise Gavin, FDA
William Gillanders, Washington University School of Medicine
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Albert Maguire, University of Pennsylvania Children's Hospital
Barbara G. Matthews, BioDirect, Inc.
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Jennifer McDonnell, Children's Hospital of Philadelphia
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Yongjie Zhou, FDA
Luis A. Zumstein, Introgen Therapeutics, Inc.

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
ADP	adenovirus death protein
AE	adverse event
AP	alkaline phosphatase
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
DHHS	U.S. Department of Health and Human Services
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
EGFR	epidermal growth factor receptor
FDA	U.S. Food and Drug Administration
hAQP1	human aquaporin-1
IR	ionizing radiation
IRB	internal review board
LCA	Leber congenital amaurosis
MTD	maximum tolerated dose
NCPHSBBR	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
NICHD	National Institute of Child Health and Human Development
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	NIH Office of Biotechnology Activities
PI	principal investigator
pu	particle unit
RAC	Recombinant DNA Advisory Committee
rAd5	recombinant serotype 5 adenovirus
RPE	retinal pigment epithelium
VCU	Virginia Commonwealth University