RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 20-21, 2002

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>.

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

June 20-21, 2002

The Recombinant DNA Advisory Committee (RAC) was convened for its 86th meeting at 8:10 a.m. on June 20, 2002, at the DoubleTree Hotel, Rockville, MD. Dr. Theodore C. Friedmann (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:10 a.m. until 5:10 p.m. on June 20 and from 8:25 a.m. until 3:40 p.m. on June 21. The following individuals were present for all or part of the meeting.

Committee Members
William E. Barkley, Howard Hughes Medical Institute
Xandra O. Breakefield, Massachusetts General Hospital
James F. Childress, University of Virginia
Neal A. DeLuca, University of Pittsburgh
David L. DeMets, University of Wisconsin Medical School
Theodore C. Friedmann, University of California, San Diego
Thomas D. Gelehrter, University of Michigan Medical School
Linda R. Gooding, Emory University
Larry G. Johnson, University of North Carolina, Chapel Hill
Philip R. Johnson, Jr., Columbus Children's Hospital
Nancy M.P. King, University of North Carolina, Chapel Hill
Sue L. Levi-Pearl, Tourette's Syndrome Association, Inc.
Maxine L. Linial, Fred Hutchinson Cancer Research Center
Robert D. Simari, Mayo Clinic and Foundation
Diane W. Wara, University of California, San Francisco

Executive Secretary
Stephen M. Rose, National Institutes of Health (NIH)

***Ad Hoc* Reviewers**
Nancy Carrasco, Albert Einstein College of Medicine
Stephen Dewhurst, University of Rochester
Ira J. Fox, University of Nebraska Medical Center
Diane E. Griffin, Johns Hopkins University
Michael Mann, University of California, San Francisco
Terry Kwan, TK Associates

Speakers
Ruth L. Kirschstein, NIH

Nonvoting/Agency Representatives
Kristina C. Borror, Department of Health and Human Services
Philip Noguchi, U.S. Food and Drug Administration (FDA)
Stephanie L. Simek, FDA

NIH Staff Members
Charla Andrews, National Institute of Allergy and Infectious Diseases (NIAID)
Sharahn Boykin, Office of the Director (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.

Sandra H. Bridges, NIAID
Scott Cairns, NIAID
Robert Chanock, NIAID
Mark Connors, NIAID
Sussan Eftekhari, OD
Kelly T. Fennington, OD
Laurie Harris, OD
Kate Heineman, OD
Valerie Hurt, NIH Legal Advisor
Michael J. Iadarola, National Institute of Dental and Craniofacial Research
Robert Jambou, OD
Bob Lanman, OD
Kathy Lesh, OD
Julius Leyton, National Institute of Arthritis and Musculoskeletal and Skin Diseases
Andrew Mannes, Pain and Palliative Care Service, Warren Grant Magnuson Clinical Center, NIH
Bonnie J. Mathieson, Office of AIDS Research
Cheryl McDonald, OD
Maureen Montgomery, OD
Marina O=Reilly, OD
Bo Peng, National Cancer Institute (NCI)
Penny Powell, OD
Alexander Rakowsky, OD
Marjorie Robert-Guroff, NCI
Stephen Rose, OD
Gene Rosenthal, OD
Rebecca Sheets, NIAID
Thomas Shih, OD
Allan Shipp, OD
Sonia I. Skarlatos, National Heart, Lung, and Blood Institute
Lana Skirboll, OD
Gisele White, OD

Others

Approximately 50 individuals attended this 2-day RAC meeting. A list of attendees appears in Attachment II.

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

Dr. Friedmann, RAC Chair, called the meeting to order at 8:10 a.m. on June 20, 2002. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on May 9, 2002 (67 FR 31353). At this meeting, the RAC reviewed six protocols and the quarterly data management report and protocol amendments and updates and discussed informed consent issues in human gene transfer research.

Dr. Rose referred RAC members to the NIH Rules of Conduct and Conflict of Interest notice provided to them in their briefing materials.

A list of abbreviations and acronyms and their meanings appears in Attachment III.

II. Discussion of Human Gene Transfer Protocol #0201-523: Phase I Trial of Intraperitoneal Administration of an Attenuated Strain (Edmonston Strain) of Measles Virus, Genetically Engineered To Produce Carcinoembryonic Antigen, in Patients With Recurrent Ovarian Cancer

Principal Investigators:	Evanthia Galanis, M.D., Mayo Clinic; Roberto B.D. Cattaneo, Ph.D., Mayo Medical School; and Jeff Sloan, Ph.D., Mayo Clinic (via teleconference)
Sponsor:	None
RAC Reviewers:	Drs. Brody, DeLuca, Gooding, and P. Johnson
Ad hoc Reviewer:	Diane Griffin, Ph.D., M.D., Johns Hopkins University

(Recusal note: Because his employer is the same university as the investigators, Dr. Simari recused himself from deliberations regarding this protocol. He did not participate in the preliminary review of the protocol, and left the room during its discussion.)

A. Protocol Summary

Cancer of the ovary is diagnosed in more than 25,400 women in the United States each year and causes the deaths of more than 14,500 women annually. Because there is no effective screening method, more than 70 percent of ovarian cancer cases are diagnosed after the tumor has already spread beyond the ovaries, and in the majority of women, the disease will recur despite aggressive initial treatment with surgery and chemotherapy. Once ovarian cancer has recurred, there are no effective treatment options. Only a minority of women responds to salvage chemotherapy, and disease progresses in most patients. There is an urgent need for innovative approaches for the treatment of recurrent ovarian cancer.

Measles virus (MV) is a ribonucleic acid virus. Although the wild-type MV can lead to a potentially serious infectious disease, attenuated (vaccine) strains of MV have an excellent safety record and have resulted in significant decreases in measles incidence and mortality worldwide. The investigation of the antitumoral properties of a vaccine strain of MV followed published reports in the literature noting that natural infection with MV had been shown to lead to the regression of other malignancies. The investigators have modified the Edmonston vaccine strain of MV to express an inert soluble marker peptide, human carcinoembryonic antigen (CEA). The construction of this novel virus variant, which retains its antitumoral effect, allows the activity of the virus to be monitored by a blood test and permitting the treatment to be better individualized. Following construction of MV-CEA, investigators have confirmed that the virus has potent antitumor activity against ovarian cancer in both laboratory cell lines and animal models. In contrast, the virus caused minimal damage in normal ovarian surface cells and in the normal lining of the abdomen.

In this study, the investigators propose to administer escalating doses of MV-CEA in the abdominal cavities of patients with recurrent ovarian cancer. When it recurs, ovarian cancer is confined in the abdomen in more than 85 percent of patients, thus making this mode of administration an attractive option in this setting. The virus will be administered up to 6 times every 4 weeks, provided the research participant has had no significant toxicity associated with the prior treatment and the disease has not progressed.

The goals of this study are to (1) find the maximum tolerable dose (MTD) of MV-CEA that can be administered in the abdominal cavity of women with recurrent ovarian cancer, (2) assess antitumoral efficacy in a preliminary fashion, (3) evaluate the body's immune response to the virus, and (4) assess the virus' effects in the body using blood, biological fluids, and tissue samples. The investigators plan to escalate the doses of the virus until the MTD is determined; a total of 34 research participants will be included in this study.

B. Reviews by RAC Members and Ad Hoc Reviewer

Drs. Brody, DeLuca, Gooding, and P. Johnson and *ad hoc* reviewer Dr. Griffin submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Brody's comments focused on the dose escalation plan, a modified version of the "cohort-of-three" design in which the next dose level can be used if the first research participant at a given dose level does not experience a grade 2 or greater toxicity. The informed consent document did not adequately explain the proposed dose-escalation scheme nor explain the modified cohort-of-three design. (Because Dr. Brody was not present at this RAC meeting, Dr. Friedmann read aloud Dr. Brody's written review.)

Dr. DeLuca offered three issues for discussion regarding this protocol: (1) the potential for subacute sclerosing panencephalitis given the proposed dose levels, (2) whether efficacy has been observed at doses lower than those at the high end of the proposed dose escalation, and (3) whether additional virus purification procedures should be performed in addition to the proposed filtration method. He questioned whether the informed consent document should compare the risks of side effects to those associated with the use of the MV vaccine, and noted that the document should clearly state that both the route of administration and the doses proposed differ significantly from those of the MV vaccine. Furthermore, while the MV vaccine has an excellent safety record, this protocol proposed to use doses three to six orders of magnitude higher than the amount of virus used in the vaccine.

Dr. Gooding noted that vaccine studies had shown that compared with conventional doses, higher doses of the Edmonston strain were associated with higher mortality rates. Increased vaccine-related mortality may be the result of measles-induced immunosuppression or immunodeviation leading to greater susceptibility to opportunistic infections. Because of the potential for dose-dependent immunosuppression by MVs, a clinical trial with a steep dose-escalation protocol is problematic. Dr. Gooding recommended a small preclinical trial with a species more susceptible to measles infection than rodents. Given the fact that MV is an effective adjuvant for production of antimeasles antibody, she also asked whether the researchers would be measuring antibody to CEA.

Dr. P. Johnson was concerned that the CEA marker may not be inert. CEA is immunogenic in mouse models of cancer vaccines. He was concerned that the high amounts of this large, soluble protein in circulation would evoke some kind of immune response. He suggested a study in outbred, immunocompetent rhesus macaques to evaluate immune responses to the transgene and the vector. Dr. P. Johnson also suggested that it would be useful to see the results of an intraperitoneal dosing study performed in macaques.

Dr. Griffin's primary concern was the effect of the proposed high doses on the immune system. She suggested that conducting studies with rhesus macaques at the high doses would offer valuable information. Dr. Griffin's other concerns included the dose escalation scheme, presence of antibody in peritoneal fluid, lack of a good explanation of a normal delayed-type hypersensitivity (DTH) response, sparse data on reimmunization, and confusion as to the meaning of "measles immunity" and "target lesions." From a public health viewpoint, she suggested that researchers immunize any potential research participants who are found to be MV nonimmune even those determined to be ineligible for participation in this clinical trial.

C. RAC Discussion

Several additional concerns were raised by RAC members. Ms. King offered sample wording to explain the dose-escalation scheme in the informed consent document. Dr. Breakefield wondered whether, at very high titer, the virus could damage the blood-brain barrier. Dr. DeLuca recommended further preclinical studies to provide more information about the effects and distribution of high-titer inoculations.

D. Investigator Response

In response to concerns about CEA being immunogenic, Dr. Galanis stated that her laboratory's many years of experience with detecting CEA in peripheral blood suggested that the soluble form of CEA proposed for use in this protocol does not result in immunity. She further explained that the virus is likely

to stay in the peritoneal cavity and not likely to circulate in the peripheral blood of immune research participants. In addition, screening will be performed to ensure that research subjects selected do not have a severe defect in their cellular immunity to MV. If subjects do not recover DTH after the first dose, they will be removed from the clinical trial.

Regarding preclinical research already conducted using macaques, Dr. Galanis described several safety studies in which nonimmune macaques were infected with four different strains of the Edmonston strain of MV. These studies resulted in no clinical illness and low levels of virus in peripheral blood cells; in addition, researchers noted no plasma viremia, no pathologic changes in lungs and liver, and no hyperplasia of organs, consistent with response to the immune stimulus. She stated that even if the researchers conducted a preclinical trial with immune macaques, the results of that trial would not necessarily change the design of the clinical trial or how carefully immunosuppression would be monitored in research participants.

Dr. Galanis agreed that what constitutes "normal DTH" in ovarian cancer patients can be difficult to determine. On the basis of available data, however, the number of subjects with low DTH response levels is not expected to be significant. The researchers are planning a pilot study to be completed before the current protocol opens for enrollment that will test DTH responses in a cohort of ovarian cancer patients.

Dr. Cattaneo summarized the consensus of the RAC members that a few macaques should be tested at the very high doses proposed for this clinical trial.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Friedmann summarized the RAC's recommendations, suggestions, and comments as follows:

- In order to better understand the safety of the proposed study, the investigators should consider conducting the same study in a non-human primate model (such as the macaque). The animal model study should also assess the "worst case scenario" and, as such, should administer repeated doses of CEA transgene at the highest dose proposed in the clinical study. The study should analyze the biodistribution of the gene transfer product, the immune response to both the measles vector and CEA, and, using RT-PCR, determine whether the vector is present in the CNS.

- A more exact description of how Delayed Type Hypersensitivity (DTH) will be measured and followed throughout the study, as proposed by the PI at the meeting, should be included in the revised clinical protocol and in the informed consent document.

- The dose escalation study design should be described in lay terms.

- The safety of administering the measles-based gene transfer vector is based on an extrapolation from measles vaccine data. The informed consent documents should clearly state that the validity of this extrapolation is not certain. Moreover, while the strain of measles that will be used is similar to the vaccine strain, the proposed doses and route of administration in this study are significantly higher than those used in vaccination and this difference should be emphasized (the highest dose proposed in this study is nearly 10^5-fold more plaqueforming units (PFU) than given in the immunization).

G. Committee Motion 1

It was moved by Dr. Gelehrter and seconded by Dr. Wara that these recommendations expressed the recommendations of the RAC. The vote was 13 in favor.

III. Discussion of Human Gene Transfer Protocol #0204-521: Inducible Nitric Oxide Synthase Gene Therapy for the Prevention of Intimal Hyperplasia in Arteriovenous Grafts Used for Hemodialysis Access

Principal Investigator:	Edith Tzeng, M.D., University of Pittsburgh Medical Center
Sponsor:	None
RAC Reviewers:	Dr. Friedmann, Ms. King, and Dr. Simari
Ad hoc Reviewer:	Michael Mann, M.D., University of California, San Francisco

(Recusal note: Because his employer is the same university as the investigators, Dr. DeLuca recused himself from deliberations regarding this protocol. He did not participate in the preliminary review, and left the room during its discussion.)

A. Protocol Summary

Patients requiring hemodialysis for end-stage renal disease experience recurrent problems with vascular access for hemodialysis. The most common vascular access is the forearm arteriovenous (AV) graft, in which a synthetic tube is placed under the skin of the forearm, with one end sewn to the artery and the other end sewn to the vein. These AV grafts often fail because of a scarring process at the point where the graft is sewn to the vein. This scarring process, known as intimal hyperplasia, is an overgrowth of smooth muscle cells that narrows the tube and leads to clot formation in the graft. This protocol is to investigate the use of gene transfer to reduce or prevent this scarring process and subsequent graft failure.

The gene for inducible nitric oxide synthase (iNOS) will be used in this protocol. iNOS is a protein that generates the active product nitric oxide which blocks smooth muscle cell proliferation and intimal hyperplasia. The gene will be delivered to the end of the vein where the synthetic graft is placed using an adenovirus (Ad). Adenovirus is one cause of colds, but the form of adenovirus to be used in this study has been altered so that it cannot reproduce itself or cause a cold. The adenovirus carrying the iNOS gene (AdiNOS) will be placed inside the segment of vein that will be connected to the graft and allowed to incubate for 30 minutes. The virus will then be removed and the graft attached to the vein.

The purpose of this proposed research study is to evaluate the safety of various doses of AdiNOS when applied to the vein-graft site in patients requiring hemodialysis. Research participants in this dose escalation study will receive a single dose of AdiNOS with the first cohort beginning with 1×10^9 viral particles and the last cohort ending with 1×10^{11} viral particles. The follow-up for this safety study will be 12 months.

B. Reviews by RAC Members and Ad Hoc Reviewer

Dr. Friedmann, Ms. King, Dr. Simari, and *ad hoc* reviewer Dr. Mann submitted written reviews, to which the investigator responded in writing and during this meeting.

Dr. Friedmann questioned whether using a first generation adenovirus, a transient expression system, would provide a sufficient anti-proliferative effect. He also noted that the pre-clinical studies to evaluate the extent and duration of vasoprotection and inhibition of intimal proliferation were of short duration, e.g., 3 days for evaluation of inflammation and 3 weeks for evaluation of intimal hyperplasia, while graft stenosis is often seen clinically much beyond three weeks. He also questioned whether there were data in animal models to evaluate the long-term effects of iNOS on hyperplasia, inflammation, and host immune response (i.e., possible cytotoxic T lymphocyte attack on transduced cells). He also asked about the possibility of significant inflammation and host immune response contributing to late “rebound” effects

such as accelerated intimal hyperplasia or predisposing the vessel wall to weakness and possible aneurysm formation.

Ms. King's comments focused on subject selection and recruitment, and the informed consent document. Ms. King offered specific comments about the informed consent document, which related to the study purpose and description, dose-escalation design, misleading terminology, risks and benefits, costs and payments, request for autopsy, and media interest in research. Ms. King noted three considerations about selection and recruitment. Decision making about the type of shunt appropriate for a particular research participant should not be influenced by the investigator's need to enroll AV graft participants. Second, potential participants should not be approached about study participation until after they have decided to undergo the AV graft procedure. Third, the member of the research team who approaches potential research participants about the study should not be someone with whom the individual has a treatment relationship. She noted that a patent was mentioned but that the patent holder was not identified.

Dr. Simari noted that none of the preclinical studies presented used the same polytetrafluoroethylene (PTFE) graft and delivery method proposed for the human study. He questioned whether the placement of the PTFE material at the site would have any effect on either pharmacokinetics or safety since this was not directly assessed in the preclinical studies. He also asked for clarification of the dose of the vector to be used. Dr. Simari questioned whether the delivery procedure would alter the standard surgical approach to AV graft placement, and whether harvesting a small piece of the vein could be done to obtain data on the pharmacokinetics and pharmacodynamics of gene delivery using this approach. Dr. Simari asked for clarification of the techniques and sensitivity of the techniques used to detect replication competent adenovirus, as well as the biosafety levels to be used in this study. Dr. Simari had concerns similar to Ms. King's about some of the language in the consent form, particularly with respect to the experimental agent being referred to as "therapy," and he suggested that any potential conflicts of interest should be more fully disclosed and discussed.

Dr. Mann raised several issues but noted that overall the protocol was very reasonably constructed to provide an evaluation of basic patient safety in an immensely large area of unmet clinical need. He requested clarification as to whether the grafts in the study will be limited to forearm grafts or whether grafts in other locations will be allowed. He noted that the preclinical studies used models of neointimal hyperplasia rather than an actual AV graft model. Since performing an animal model of AV grafting is a huge undertaking, he did not feel this was absolutely necessary given the information known about iNOS. However he noted that it should be clear in the consent form that animal studies did not exactly reflect the procedure that will be done clinically. Dr. Mann emphasized that while the preclinical studies addressed the question of neointimal hyperplasia as a biological phenomenon, AV graft failure is a multi-factorial and complex biological phenomenon. Due to this, in this small, uncontrolled Phase I study, it would be impossible to make any real conclusions about the efficacy of the investigational agent and safety is the primary endpoint. The elements that the protocol outlines as measurements of the secondary endpoint of efficacy should really be considered measurements of feasibility. Dr. Mann suggested that three of the proposed efficacy endpoints: percent stenosis, time to thrombosis, and time to first intervention, be viewed as safety elements and be included in the primary endpoint. Also, Dr. Mann suggested that in order to minimize subjectivity, objective criteria for what constitutes "poor arm veins" as referred to in the protocol should be delineated. Like Dr. Simari, Dr. Mann noted that there is at least a theoretical possibility that replication competent adenovirus might be administered and actually stimulate neointimal hyperplasia. In response to Dr. Simari's question about obtaining vein tissue at the time of surgery, Dr. Mann recommended not obtaining tissue. If a very small piece of tissue were obtained, it would be stretching the limits of current technology to perform any sort of reproducible analysis on it. On the other hand, a side branch large enough for testing might compromise venous return by removing the potential route of venous return provided by the side branch.

C. RAC Discussion

Two other concerns were raised by RAC members in addition to those expressed by the initial reviewers:

Dr. Friedmann suggested that the RAC would find it useful to receive some information from this protocol's institutional biosafety committee (IBC) regarding the nature of the discussion about BSL-1 and BSL-2 containment conditions. Dr. Larry Johnson asked Dr. Tzeng whether the 30 minutes that the vessel is clamped for instillation of the vector could possibly affect the integrity of the endothelium.

D. Investigator Response

With respect to Dr. Friedmann's points, Dr. Tzeng noted that long-term follow-up in pig models is logistically difficult given their rapid growth and size. Realizing that there are limitations to the rodent model, she suggested that the six weeks studies in the rat should hopefully answer some of the questions about long-term follow-up.

Dr. Tzeng noted that no evidence of inflammation was seen in the vein grafts of the rodent or pig studies, including those in the highest dose group. This may be due to the purity of the virus preparations used as well as a relatively low dose, but also nitric oxide is known to be anti-inflammatory. Dr. Phil Johnson asked how did the investigators account for the decrease in the transgene expression over two weeks seen in the animal models if there was no inflammatory response to remove the transduced cells. Dr. Tzeng postulated that because there is remodeling going on in the vein grafts, part of the reduction in transgene expression might be due to a dilutional effect. Also, the CMV promoter can deregulate, causing reduced expression over time. Dr. Johnson noted that in an adenoviral vector, it would be unusual for the CMV promoter not to be active for greater than two weeks, and considering the lack of inflammatory response, the decrease in transgene expression seems unexpected.

With respect to Ms. King's comments, as well as those of other reviewers, Dr. Tzeng replied that all of the suggested changes to the informed consent document had been made.

With respect to potential conflict of interest issues, Dr. Tzeng stated that her husband is listed on the patent for the iNOS cDNA and that she herself is on the use patent for iNOS cDNA as a gene therapy. Both she and her husband are in the process of eliminating all financial ties to this potential therapy and this clinical trial is independent of any corporate sponsorship. GenVec, Inc. has licensed the use of this cDNA for applications of vascular gene therapies, however GenVec, Inc. has not been involved with this trial according to Dr. Tzeng.

Dr. Tzeng explained that the Institutional Review Board (IRB) at the University of Pittsburgh requires that a Principal Investigator on a study approach patients about the possibility of participating in the study. She suggested that perhaps a research nurse could first approach the patients about the study and if they are interested, the vascular surgeon could actually answer questions about the study. She will confer with the IRB with this proposal.

In response to the questions of Dr. Simari and Dr. Larry Johnson, Dr. Tzeng responded that the surgical procedure for gene transfer is identical to the standard procedure, and most injuries to the vein occur during the dissection process, so the additional 30 minutes of isolating the vein and instilling the vector is not likely to add to the vessel injury. She also noted that she did not expect that the foreign body, the PTFE graft, would alter the expression of the iNOS or alter the safety. They did not see any breakdown of anastomosis breakdown or aneurysm formation in the pre-clinical models.

With respect to questions about the biosafety level to be used in this protocol, Dr. Tzeng clarified that the reference to BSL-1 levels in the protocol was meant to reflect that once a subject is outside of the medical care institutions, one cannot guarantee the BSL-2 containment. However, BSL-2 conditions will be employed in the operating room and universal precautions will be employed when subjects are undergoing dialysis and if they are subsequently hospitalized.

E. Public Comment

Dr. Joe Glorioso offered that gene expression could be lost for a number of reasons, for example the induction of cytokine genes such as IL-6 will shut off the CMV promoter without the inflammatory response.

F. RAC Recommendations

Dr. Friedmann summarized the RAC's recommendations, suggestions, and comments as follows:

- To maximize the safety of the protocol to research participants, the primary endpoints for this protocol should include: 1) determination of the time to thrombosis of the AV graft; 2) the time to first intervention for stenosis of venous anastomosis; and 3) the determination, by fistulography, of the percent stenosis at the venous anastomosis at 6 and 12 months.

- The protocol and informed consent documents should be revised to make clear that graft placement is limited to the forearm. Also, in order to minimize the element of subjectivity in research participant selection, the protocol, in the exclusion criteria, should delineate objective measure(s) of what constitutes a "poor arm vein."

- The informed consent documents should include information about reproductive precautions male research participants should employ.

- The protocol should clearly delineate the recruitment process for research participants. Consideration should be given to the following or similar approach. A provider with whom the potential enrollee has a direct treatment relationship should be the first point of contact with the potential research participant about participation in the study. An individual without a direct patient care relationship with the potential research participant should review the study with the potential research participant and carry out the informed consent process. This will help separate the research from treatment and maximizes the voluntary nature of decisions about participation in the research study. This precaution would not preclude the principal investigator(s) providing specific information to assist potential research participants in the decision-making process.

- The informed consent documents should clearly state that the AV graft to be used in the clinical study is not exactly the same as the one tested in the animal model studies and that extrapolation of the available animal data to humans might not be valid.

- As a Phase I study, all references to "therapy" or "efficacy" should be changed to "gene transfer."

- The informed consent documents should describe the potential of replication competent adenovirus being administered and the possibility that graft function may worsen.

G. Committee Motion 2

It was moved by Dr. L. Johnson and seconded by Dr. Simari that these recommendations expressed the comments and concerns of the RAC. The vote was 13 in favor, with one abstention (Ms. Levi-Pearl).

IV. Minutes of the March 7-8, 2002, RAC Meeting/Ms. Levi-Pearl

Ms. Levi-Pearl noted that the minutes were an accurate reflection of the March 2002 RAC meeting, with one minor change: In the last sentence on page 8, section E, "Ms. King will be…" should be changed to "Ms. King and Dr. Brody will serve as co-chairs of this working group."

A. Committee Motion 3

As moved by Ms. Levi-Pearl and seconded by Dr. Simari, the RAC accepted the March 7-8, 2002, minutes, as amended, by a vote of 15 in favor of the motion.

V. Discussion of Human Gene Transfer Protocol #0201-528: Pilot Study of the Use of the Human hSlo/maxi-K Gene To Treat Erectile Dysfunction

Principal Investigator:	Arnold Melman, M.D., Albert Einstein College of Medicine, George J. Christ, Ph.D., Albert Einstein College of Medicine, and Kelvin Davies, Ph.D., Albert Einstein College of Medicine
Sponsor:	None
RAC Reviewers:	Drs. Childress and Gelehrter
Ad hoc Reviewers:	Ira J. Fox, M.D., University of Nebraska Medical Center; John J. Mulcahy, M.D., Indiana University School of Medicine (via teleconference); and Mark T. Nelson, Ph.D., University of Vermont (via teleconference)

A. Protocol Summary

Erectile dysfunction (ED) affects about 35 million men in the United States with approximately fifty-two percent of men between the ages of 40 and 70 having some degree of erectile dysfunction. Over the past 30 years, the treatment of ED has evolved from a primary reliance on invasive surgery to the use of repetitive, on-demand injections, and most recently, to the use of an oral medication. However, there are drawbacks, including limited efficacy and the potential for serious side effects, to each of these modalities.

Potassium channels regulate the smooth muscle cell spasm/contraction of the penis by decreasing the activity of calcium channels and reducing the entry of calcium ions into the cell. Lowered levels of intracellular calcium allow for decreased smooth muscle contraction and greater smooth muscle relaxation, thereby allowing rigid erections to occur.

This proposed protocol is a Phase I safety study in which a non-viral gene transfer vector containing the gene for a potassium channel will be used. The approach will involve a single injection of the gene transfer vector into the cavernosum of the penis that will direct the insertion of functional potassium channels in the membranes of the smooth muscle cells lining the cavernosum. The cells affected by the gene transfer are expected to express increased amounts of the protein that either forms potassium channels or results in the formation of a more active potassium channel in the cell membrane. In either case, the relaxation of the smooth muscle cells would be enhanced, the cell spasm/contraction would be overcome, and erectile function would be improved.

Preclinical animal studies showed that erectile function could be restored for an extended period of time following a single administration of the vector. In the clinical study, research participants are to be followed for 6 months and evaluated using the International Index of Erectile Function questionnaire, which will assess the ability of subjects to engage in sexual intercourse with their partners, as well as with a Rigiscan™ device for the measurement of visual sexual stimulation and sleep-induced erection.

B. Review by RAC Members and Ad Hoc Reviewers

Drs. Childress and Gelehrter submitted written reviews, as did *ad hoc* reviewers Drs. Fox, Mulcahy, and Nelson, to which the investigators responded in writing and during this meeting.

Dr. Childress focused his review primarily on the ethical and social issues raised in this protocol. He had several comments regarding the consent form, most of which were addressed by the investigators prior to the meeting. He noted some inconsistencies in wording between the consent document and the protocol particularly with respect to the number of visits and the duration of follow-up; the need for fuller financial

disclosure information; the use of the word “treatment” in the consent form; the need to include a request for autopsy in the protocol and consent; the need for clarification of the use of barrier contraceptive measures; and the need for an informed consent document for the partner. Regarding the selection of participants, Dr. Childress asked the investigator why participants would be limited to heterosexual couples and why individuals with mild-to-moderate ED were preferred over subjects with lesser or greater degrees of erectile dysfunction. Dr. Childress also raised the larger philosophical question of how one begins to draw a line between “therapy” and “enhancement.”

Dr. Gelehrter noted that while ED is a significant and distressing disorder, it is not life-threatening and therapies, albeit imperfect, are available. As such he suggested that the assessment of safety should be the primary clinical endpoint in this Phase I study. Yet he noted confusion in the protocol between safety and efficacy as a primary clinical endpoint and this confusion carries over to the informed consent document. Even though the injection is localized to the penis, it is effectively an intravenous injection, and, as such, Dr. Gelehrter felt that the parameters for assessing the safety and toxicity were somewhat limited. Because ion channels are affected, there are concerns about various other contractile tissues, and he asked whether bowel and bladder function would be monitored during the study. Dr. Gelehrter also questioned the applicability of the streptozocin-induced diabetic rat model to man and asked Dr. Melman to clarify his comments on the aging rat model.

Dr. Fox also questioned whether the streptozocin-induced diabetic rat model was appropriate for addressing diabetic related erectile dysfunction, but noted that the aged rat model was quite good. He asked whether using sildenafil could reverse the processes in these two model systems. In his written review, Dr. Fox noted the discrepancy between the rapid elimination of the plasmid and the maintenance of the physiologic effect. Dr. Melman submitted additional information during preliminary review, which Dr. Fox felt was helpful in showing that the gene was at least present during the period of time when the effect was noted. He also questioned how long will it take for gene expression to begin and whether the planned three-hour observation of subjects post-administration would be long enough to detect all systemic toxicities. In response to Dr. Fox’s concerns about assessing toxicity issues in the rat models, the investigators proposed dog studies. Dr. Fox felt that these would be significantly more useful to address questions about potential toxicities, especially cardiovascular toxicities, than rat studies. Also, given the potential toxicities and systemic effects, he felt that the population group should be subjects with moderate ED rather than mild ED.

With respect to the informed consent document, Dr. Fox felt it should contain a more detailed discussion of the types of therapies that might be required to treat potential adverse events. He agreed with the other reviewers that the informed consent document should have a section on autopsy request and that the enrollment process and monitoring system needed mechanisms to avoid any real or perceived conflicts of interest issues.

Dr. Mulcahy was asked to review this protocol regarding potential applicability to clinical urologic practice, specifically in the field of erectile dysfunction. In his opinion, much of the reluctance of patients to proceed with treatment for ED is due to the invasiveness and aggressiveness of therapies other than sildenafil. Only sixty percent or so of patients respond to sildenafil, so there is a large clinical need for other therapies, and were this approach to be successful it would be an advance in the field. Dr. Mulcahy noted that urologists have been using injections of medications into the penis for almost 20 years. He addressed some of the concerns about potential effects on adjacent organs such as the prostate, bladder, testicles, and seminal vesicles by reviewing the blood flow in the penis. The penis is an end-organ for arterial blood flow and even if the vector was injected into the corporal artery inadvertently, these adjacent structures would not be exposed to that arterial blood. Whatever is injected into the penis and not taken up by the cells locally would ultimately be taken up by the venous drainage system and emptied into the vena cava and diluted in the systemic circulation. Although the risk is unlikely if an experienced urologist is involved, Dr. Mulcahy asked what toxicities might be expected if the investigational agent were inadvertently injected subcutaneously.

Dr. Nelson began by disclosing that Dr. Christ had asked him to consider being on a protocol review committee, but that, thus far, such an arrangement had not developed. In his review of the protocol for

the RAC, Dr. Nelson focused on smooth muscle ion channels, his area of expertise. He noted that the human large-conductance, calcium-dependent ("Maxi-K or BK") channel is expressed in all smooth muscle, but not in cardiac muscle. The BK channel is activated by membrane potential depolarization and an elevation in intracellular calcium, but it is also activated by cGMP-dependent protein kinase and, thus, stimulated by nitric oxide. It can, therefore, play an important role in smooth muscle relaxation in response to the nitric oxide derived from nerves and endothelium, leading to penile erection. Because of the local injection of the cDNA (hslo) plasmid into the corpus cavernosum, Dr. Nelson considered it was unlikely that significant amounts of the plasmid would reach and be incorporated into the vasculature or the heart. However, if the approach were to lead to small elevations in the expression of the BK channel in blood vessels, it would seem unlikely that it could alter blood pressure. The channel itself serves as a negative feedback element to respond to membrane potential depolarization and increases in intracellular calcium. Thus, a slight over-expression would likely have little effect on vascular function since the activity of the channel would decrease with membrane potential hyperpolarization and a reduction in calcium. With respect to any potential effects on the urinary bladder, he suggested that the chances of it reaching the bladder were slight, but even if it did, it would not affect bladder instability. Rather, the likely effect if it reached the bladder would be to decrease instability, in fact, these types of approaches are being studied for treatments of incontinence.

C. RAC Discussion

Other concerns raised by RAC members are as follows:

- Dr. Breakefield re-emphasized the importance of taking a cautious approach to the development of a gene transfer modality to be used for a non-life-threatening condition. She asked for clarification from the investigator as to the actual administration of the agent and the risk of priapism.

- Dr. Friedmann asked whether the investigators were estimating the stability of the plasmid DNA based upon literature reports or on their own stability studies in the animal models. He also asked the investigators about the state of the plasmid in the tissues injected, i.e., integrated or episomal.

- Dr. Gelehrter asked the investigators whether in the diabetic and aging rat models, there was a reduction in the actual number of ion channels or merely a decrease in the functioning of the channels.

- Dr. Simari asked whether the duration of expression data included controls for DNA contamination and whether the detection was specific for the transgene versus the native gene. He also suggested that the proposed dog studies to evaluate potential cardiac toxicities should include assessments of arrhythmias and be designed in consultation with a cardiac electrophysiologist experienced in animal modeling.

- Ms. Levi-Pearl suggested that in order to fully inform potential subjects, the informed consent document be continually updated concerning any significant adverse events experienced in previously enrolled subjects.

D. Investigator Response

Dr. Melman pointed out that there is a general misperception that erectile dysfunction is not a medical problem but rather a quality of life issue. Erectile dysfunction is a disease that causes depression, affecting productivity and personal well-being, and is often a marker for more serious systemic diseases.

Dr. Melman worked in consultation with ethicists at Albert Einstein, Drs. Nancy Dubler and Ruth Macklin, to improve the protocol and consent process based on the comments from the RAC preliminary review. These included extending the trial to one year and the follow-up to 15 years; creating a separate consent form for the partner; clarifying that Dr. Melman's financial interest as the owner of Ion Channel Innovations; and adding the recommendation that condoms be used as a barrier contraceptive for female partners of childbearing potential.

In response to the questions about the exclusion of homosexual subjects, Dr. Melman explained that the International Index of Erectile Function (IIEF) to be used in this study has only been validated for heterosexual men and heterosexual couples.

Regarding Dr. Gelehrter's question about monitoring bowel and bladder function, Dr. Melman stated that he did not plan to do formal urodynamic evaluations on the subjects. Rather, they will determine a pre-study symptom score and will ask participants questions about any alterations in bowel and bladder functioning throughout the study.

Dr. Christ responded to the questions about the applicability of the STZ rat model and the changes seen in the aged rat model. He noted that the animals were diabetic for two months and had documented frank axonal neuropathy, similar to what is seen in humans, prior to receipt of the gene product. They were then followed for six months. While this model cannot reproduce all human diabetic conditions, there are several publications that demonstrate that at the six-month time point, the vascular, endothelial and neuropathic changes in the STZ diabetic animal become more analogous to the human condition. The aging and diabetic rat models were designed to study the loss of effector nerves and determine whether normal function could be restored by altering the sensitivity of the smooth muscle cells (by over expression of the potassium channel).

With respect to concerns about conflict of interest, Dr. Melman explained that once a potential research participant has been identified, that person will be referred to a nurse practitioner for more information about the study. Because the nurse practitioner works for him, Dr. Melman agreed to have an employee from outside his department initially speak to the patient about the study. However, Dr. Melman noted that because he is the urologist with the most knowledge about the protocol he is best suited to answer questions and concerns about the study.

In response to Dr. Mulcahy's question about what might happen if the agent was inadvertently injected into the subcutaneous tissue, Dr. Melman postulated that the plasmid would be degraded and at most there may be a local inflammatory response. However, he noted, and Dr. Mulcahy agreed, that a misdirected injection was unlikely if an experienced urologist administered the injection. With respect to concerns about priapism, Dr. Melman noted that in four years of animal testing, they saw no cases of priapism. Rather, they found that as soon as the stimulus was turned off, there was reversal of effect and detumescence. Also, they have done animal studies in conjunction with other drugs and have also not seen priapism. The channel has a very signal specific activation and in man, the stimulus sexual. When the sexual stimulus is "turned off", the channel closes and the effect reverses. In the unlikely event that priapism occurs, treatments involving alpha agonist drugs or, a shunt in the penis are available. The informed consent document includes this information.

With respect to the questions about estimating the stability, state of the plasmid, and expression data, Dr. Christ responded that stability studies on the DNA had not been done, but could be. Assessing how many cells out of a particular tissue section were transfected has been more difficult due to a lack of antibody to the Maxi-K channel. Dr. Davies has recently developed a GFP fusion protein for hSlo that will allow them to better assess this issue.

Dr. Melman agreed with Ms. Levi-Pearl's suggestion of keeping the informed consent document up-to-date with respect to previously seen adverse events.

E. Public Comment

Dr. Joe Glorioso noted that experience in the field suggests that it has been very difficult to get long-term gene expression from plasmids, and asked the investigators whether they had any quantitative data on the level and persistence of gene expression in the tissues. Dr. Davies responded that they detected the transcript to the six-month time point. Dr. Glorioso questioned how they knew they weren't detecting endogenous transcripts. Dr. Davies responded that the RT-PCR reaction was designed to distinguish the plasmid transcript, but they did not have quantitative data.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations and observations:

- Potential problems that could affect the safety of the research participants were identified with the current biodistribution data for the plasmid. Since plasmid is to be delivered into a highly vascularized tissue, systemic dissemination is possible even with the use of a tourniquet for ten minutes after administration. Preclinical biodistribution studies should therefore be designed to examine the effects of both local administration and deliberate systemic administration. To more fully address potential safety concerns about systemic dissemination, particular emphasis should be placed on examining other tissues in which alteration of calcium/potassium ion channel functioning might interfere with or modify vital conduction systems, such as in the heart or skeletal muscle. In order to more carefully examine potential cardiac safety concerns, studies should be considered in a canine model developed in consultation with a cardiac electrophysiologist experienced in that animal model. The outcome of discussions between the investigator and the Institutional Review Board regarding this issue should be conveyed to OBA.

- The dogs in the preclinical studies should be followed for a period long enough to allow detection of long-term cardiac or other muscle dysfunction. This is important given concerns about the possibility of uptake in the myocardium and/or conduction system with possible long-term gene expression. Additionally, targeted electrophysiological studies in the dog, similar to those performed in human patients, that will stress the cardiac conduction system to reveal potential conduction system toxicities are highly recommended.

- DNA contamination cannot be ruled out and gene expression cannot be convincingly demonstrated in the animal studies since no concomitant RT-negative controls were performed in the RT-PCR experiments analyzing the location and duration of gene expression. More extensive RT-PCR studies, using appropriate controls, should be conducted to characterize both the site and duration of gene expression.

- Inverted PCR studies in a suitable animal model were recommended to look for integration. Further studies should include careful tissue analyses to elucidate the physical state of the plasmid in the cells and to determine whether there is evidence of a host immune inflammatory response.

G. Committee Motion 4

It was moved by Dr. Childress and seconded by Dr. Gelehrter that these recommendations expressed the recommendations of the RAC. The vote was 13 in favor.

VI. Discussion of Human Gene Transfer Protocol #0201-529: Gene Transfer for Intractable Pain: A Phase I Clinical Trial To Determine the Maximum Tolerable Dose of a Replication-Defective Human Herpes Simplex Virus Vector Expressing Human Proenkephalin

Principal Investigators:	David Fink, M.D., University of Pittsburgh School of Medicine, and Joseph Glorioso, Ph.D., University of Pittsburgh School of Medicine
Sponsor:	None
RAC Reviewers:	Dr. Breakefield, Ms. Levi-Pearl, and Dr. Wara
Ad hoc Reviewers:	Howard Federoff, M.D., Ph.D., University of Rochester (written response), and Bernard Lo, M.D., University of California, San Francisco (via teleconference)

(Recusal note: Because he is from the same university as the investigators, Dr. DeLuca recused himself from deliberations regarding this protocol. He did not participate in the preliminary reviews and left the room during its discussion.)

A. Protocol Summary

Up to 80 percent of patients with cancer ultimately suffer from chronic pain, the most common cause of which is tumor that has spread to bone. Although analgesics are effective early in the course of the disease, high doses of narcotic analgesics are needed. However, there are significant side effects that affect quality of life and limit dosage that can be administered. Analgesics act through receptors for naturally-produced opioid peptides. Although the existence of natural opioid peptides has been known for more than 25 years, these peptides have not yet been adapted for therapeutic purposes because of their short half-life and difficulty in administration.

The investigators have created a recombinant gene transfer vector based on the human herpes simplex virus (HSV). In its naturally occurring form, the virus causes cold sores. The recombinant vector has been modified in two ways. Critical genes have been removed from the virus so that it cannot reproduce itself, and a gene coding for an opioid peptide (proenkephalin) has been inserted into the modified vector. Animal studies have shown that inoculation with this vector provides an analgesic effect in several different models of pain, including pain caused by cancer in bone.

Targeted delivery and expression of endogenous opioid peptides in the nervous system by gene transfer is a strategy to exploit the use of these natural peptides as analgesic agents. The unique targeting properties of HSV-based vectors allow efficient uptake at the dorsal root ganglia (DRG) neurons from the peripheral inoculation and provide a means for directing expression and release in the spinal cord. The non-replicating HSV vector-expressing human proenkephalin transduces DRG after subcutaneous inoculation and reduces the pain-related behavior in animal models of inflammatory pain, neuropathic pain, and pain caused by cancer

In this study, the investigators plan to test the safety of the new vector in 18 research participants with cancer that has metastasized to the bones of the spine, causing severe untreatable pain in that region. The vector will be injected under the skin, and the research participants will be followed for adverse effects and response to the experimental treatment. The study will follow a standard Phase I dose-escalation scheme, with three to six research participants treated at each dose level and dose levels that increase in half-log increments.

B. Reviews by RAC Members and Ad Hoc Reviewers

Dr. Breakefield, Ms. Levi-Pearl, Dr. Wara, and *ad hoc* reviewers Drs. Federoff and Lo submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Breakefield stated that the deletion of two genes essential for viral replication suggested that this HSV recombinant vector is likely to be reasonably safe at the doses and route of injection proposed. She expressed concern about the applicability of preclinical models (in which vector was injected into animals' paws) to human experience, in part because humans have fewer nerve endings in the back, and as a result, efficient delivery may be reduced. Dr. Breakefield asked whether transgene product acts as a narcotic and whether, if injected into the brain, it would produce affects similar to morphine, resulting in an addictive state. She noted that determination of persistence would need to wait until autopsy and that determination of transgene expression would have to be determined by pain parameters, which are often subjective.

Ms. Levi-Pearl focused her review on informed consent issues. Overall, she noted that the proposed research participant population is likely to be among the most desperate and the most vulnerable to unrealistic expectations from this Phase I study. She, therefore, suggested that extra care must be taken to ensure that research participants understand that this experiment may not result in a reduction in the research participant's pain. Ms. Levi-Pearl noted that the language is not written at the level of a lay

reader and that a thorough proofreading of the document is needed. She also added that a description of the dose-escalation scheme should be included and that participants should be made aware of all AEs experienced by earlier enrollees. She referred investigators to Appendix M of the *NIH Guidelines* for the appropriate phrasing for the autopsy permission request.

Although Dr. Wara suggested that a study of chronic pain in a macaque animal model prior to initiation of this protocol would be useful, she acknowledged this would be difficult to achieve because of significant regulatory issues. She asked that the investigators describe the methodologies for evaluating dermatome-specific pain in the research participant cohort and how the screening pain assessment instrument and the standardized assessment booklet would address evaluation of this type of pain. Dr. Wara also requested more information regarding the investigators' previous experience with subcutaneous dermatome injection of an analgesic, how the expressed and released proenkephalin will be evaluated, and the advantages of defining the immune status of the research participant prior to enrollment (e.g., whether participants with decreased CD4 cells [less than 350 cells/dl] and/or no evidence of delayed hypersensitivity by skin test should be excluded).

Dr. Federoff pointed out the need for the further data about whether (1) delivery via subcutaneous or other peripheral administration routes results in anatomically circumscribed expression of proenkephalin, (2) whether localized proenkephalin does not result in reorganization of the afferent pathway within the spinal cord, and (3) the mechanism of loss of the antinociceptive benefit of proenkephalin gene expression. He recommended that the investigators consider the immune status of each research participant prior to enrollment (e.g., patients on chronic steroids should be excluded and the need to be only 21 days out following chemotherapy or radiotherapy needs to be better rationalized in terms of the patient's immune system). He was concerned that the expression of proenkephalin may lead to a high level of neuropeptide production. It would be important to know whether the high level of expression of this peptide as well as the high level of expression of ICP0 can produce damage to the dorsal root ganglion.

Dr. Lo suggested that a patient advocate might be useful in the consent process and advised investigators to be alert for unexpected AEs that might be minor on the surface but might signal more serious problems. He asked how the followup data would be assessed and by whom, and what therapies were proposed if complications occur. He suggested that the pain assessment instrument be validated for assessing response to therapy at a specific site (not simply pain in general). He asked about the measurements of expression of the proenkephalin gene. He also asked about assessment by a radiation oncologist of the advisability of radiation therapy for symptom relief or to prevent additional complications, and whether use of naloxone (to reverse opiate related neurological complications) would likely precipitate opioid withdrawal in participants requiring chronic opioids for analgesia. Dr. Lo also expressed concern about (1) the need to ensure that research participants understand that safety is the primary goal of this Phase I study; (2) the need for more explanation about the informed consent process and a means for determining whether potential research participants have adequately comprehended the document, (3) omitting such words as "therapy" and "treatment" in the informed consent document, (4) describing the risks of the study in a realistic way, and (5) discussing potential conflicts of interest.

C. RAC Discussion

Ms. King suggested using a form of consent monitoring in which a followup telephone call is made to new enrollees. The caller/consent monitor asks the new enrollee a few key questions, and if the consent monitor is not completely satisfied that the research participant understands the aim of the protocol, the monitor informs the investigator that the enrollee needs more information. Ms. King noted that Dr. Benjamin Wilfond, Head of the Section on Genetics, Department of Clinical Bioethics, Warren Grant Magnuson Clinical Center, NIH, had designed such a monitoring system.

Ms. King noted that many of the suggestions she and other RAC members were making are spelled out in Appendix M-III of the *NIH Guidelines*, and that IRBs may not realize that compliance with Appendix M is required.

Dr. Rose reiterated the Office of Biotechnology Activities' (OBA) willingness to confer with any IRB member or chair about Appendix M issues.

D. Investigator Response

Dr. Fink explained that for this Phase I safety study all research participants will have back pain secondary to metastases to a vertebral body, but not necessarily to the same vertebral body. A Phase II study of efficacy would likely restrict research participants to those with a single, similar vertebral metastasis and pain in that region.

Dr. Fink emphasized that the investigator wish to make the protocol and consent process as understandable as possible for potential research participants, and that the guidance provided by the RAC would be followed.

Dr. Fink agreed with Dr. Federoff's concern about the importance of investigators considering the immune status of patients, especially those patients taking steroids, and, therefore, consulted with Dr. Richard J. Whitley, an expert on clinical herpes infection. Patients in treatment are likely to be severely immune suppressed. However, common reactivations appear as skin disease, which can be treated with acyclovir. Dr. Whitley advised that potential research participants should be screened for low CD4 counts or low immunoglobulin gamma levels and should be excluded from this clinical trial.

E. Public Comment

Joann C. Delenick suggested that the investigators add a supplementary information packet to the information materials approved by the IRB.

F. RAC Recommendations

Dr. Friedmann summarized the RAC recommendations as follows:

- The use of a consent monitor may help enhance a research participant's understanding that this is a phase I safety study and not intended to cure the research participant's pain. Examples of how consent monitors have been used successfully in other studies are available from OBA.

- As written, the document overstates the potential benefits. The informed consent documents should clearly state that the protocol is a phase I safety study with no intended benefit to the research participants.

- The number of research participants to be enrolled in each dose escalation cohort of the study should be stated included in the informed consent document.

- The document is overly technical and should be written in lay language. This is especially true in the description of the dose escalation study design. An example is available from OBA if desired.

- An explicit statement should be added that the research participant may withdraw from the research protocol at any time without jeopardizing their ability to receive conventional treatment.

- The stated amount of vector used in the study should be the same as it is in the protocol.

- Language found in Appendix M of the *NIH Guidelines* should be used as a guide for the section requesting consent for autopsy.

- Current or potential financial interests the investigators have in this protocol should be disclosed.

G. Committee Motion 5

It was moved by Dr. Gelehrter and seconded by Dr. Wara that these recommendations expressed the recommendations of the RAC. The vote was 14 in favor.

VII. Day One Adjournment/Dr. Friedmann

Dr. Friedmann thanked the participants and adjourned the first day of the June 2002 RAC meeting at 5:10 p.m. on June 20, 2002.

VIII. Day Two Opening Remarks/Dr. Friedmann

Dr. Friedmann opened the second day of the June 2002 RAC meeting at 8:25 a.m. on June 21, 2002.

IX. Informed Consent Working Group Report/Ms. King

Ms. King presented a report of the work plan for this group. Chaired by Ms. King and Dr. Brody, the group's members include RAC members Dr. Childress, Dr. Lo, Dr. Wara, Ms. King, and Ms. Levi-Pearl; Dr. Patterson and Mr. Shipp, OBA; Dr. Kristina C. Borror, Office for Human Research Protections; and Dr. Philippe Bishop, FDA. Although both Ms. King and Ms. Levi-Pearl will be stepping down from the RAC after this meeting, Ms. King noted that she and Ms. Levi-Pearl have agreed to continue as members of this working group. The goal of the working group is to create an item-by-item annotation of Appendix M-III in the *NIH Guidelines.* For each subsection of Appendix M-III, the working group will offer examples of appropriate and inappropriate language, references, and links to articles on a particular issue. Information to be gathered includes model informed consent documents and other relevant materials. Ms. King invited RAC members, investigators, IRBs, and sponsors involved in gene transfer research to submit relevant materials to the working group.

Dr. Brody will keep the RAC apprised of the working group's progress

X. Induction of New RAC Members and Presentation of RAC Member Certificates/Ruth L. Kirschstein, M.D., Deputy Director, National Institutes of Health

After reviewing discussed the establishment, history, and continuing importance of the RAC, Dr. Kirschstein, on behalf of Dr. Elias Zerhouni, NIH Director, administered the oath of office to three new RAC members. The new RAC members are Drs. Neal DeLuca, W. Emmett Barkley, and Thomas Gelehrter.

Dr. Kirschstein presented certificates to retiring RAC members and thanked them for their service to the RAC, to the Federal Government, and to the NIH. The retiring RAC members are Dr. Breakefield, Ms. King, and Ms. Levi-Pearl.

XI. Discussion of Human Gene Transfer Protocol #0112-533: Phase I Trial of *in situ* Gene Therapy for Locally Recurrent Prostate Cancer Following Radiation Therapy Failure Using Sodium/Iodide Symporter and Radioiodine

Principal Investigator:	John Morris, M.D., Mayo Clinic
Sponsor:	None
RAC Reviewers:	Drs. Childress, Friedmann, and L. Johnson
Ad Hoc Reviewers:	Nancy Carrasco, M.D., Albert Einstein College of Medicine, and Paul Ladenson, M.D., Johns Hopkins Medical Institutions (via teleconference)

(Recusal note: Because his employer is the same institution as the investigators, Dr. Simari recused himself from deliberations regarding this protocol. He did not participate in the preliminary reviews of the protocol and left the room during its discussion.)

A. Protocol Summary

Most patients with thyroid cancer, including those with metastatic deposits of tumor, have a good prognosis if treated with radioiodine therapy. Radioiodine is currently used only for thyroid cancer. Thyroid cells have an iodide transporter (called the sodium-iodide symporter or NIS) that allows them to concentrate iodine from the blood stream. This study proposes to insert the gene for the NIS into prostate cancer cells so that they too may be treated with radioiodine.

The study population will be men with prostate cancer that has recurred locally in the pelvis after external beam radiation therapy. Research participants will be administered a vector expressing the NIS gene by direct injection into the prostate during a procedure requiring general anesthesia. If the NIS gene is expressed, the symporter should function to take iodine into the cells. Three days after the injection the men will be given a small tracer dose of radioactive iodine in order to measure radioiodine uptake within the prostate. If the amount is sufficiently high, on Day 4 the participants will be given a therapeutic dose of radioiodine. The research participants will be carefully observed in the Clinical Research Unit for any possible toxic effects of the vector and radioiodine, as well as for any tumor responses to the therapy.

Because the thyroid may also be affected by the radioiodine therapy, the research participants will be given thyroid hormone prior to treatment in order to block uptake of radioiodine by the thyroid. Thyroid function will be monitored carefully and if a decline in function occurs, thyroxine replacement therapy, standard treatment of hypothyroidism, will be administered.

B. Written Comments From Preliminary Review

Drs. Childress, Friedmann, and L. Johnson and *ad hoc* reviewers Drs. Carrasco and Ladenson submitted written reviews, to which the investigator responded in writing and during this meeting.

Dr. Childress considered the risk assessment to be the critical issue in this protocol. He noted a few discrepancies between the informed consent document and the protocol and asked whether general or spinal anesthesia would be used, what the recommendation would be regarding contraception (timeframe and specific suggested form), and the total number of men who would take part in this study. Dr. Childress noted that the risk involved in administering the anesthesia should be mentioned in the informed consent document. He also suggested a separate heading for “Request for Autopsy” and clearer language about whether a family member can give consent for autopsy.

Dr. Friedmann asked about the efficiency of blockade of thyroid uptake and the potential for thyroid damage from the therapeutic dose of 131-iodine. He noted that no data were presented to show the degree of uptake blockade by levothyroxine (T3) in other NIS-expressing organs such as the gastric and colonic mucosa, salivary glands, and kidneys. He suggested that careful biodistribution and gene expression studies together with circulating virus titers after local injection might help to establish what level of concern would be appropriate related to radiation dosage and transduction of ectopic tissues.

Dr. L. Johnson questioned what data had been gathered from multiple studies of prostatic cancer regarding the relative frequency and types of toxicity from administration of adenoviral vectors alone. He questioned whether there was any amplification of adenoviral-specific toxicity by the radiation effects. He asked about the success rate of brachytherapy in resistant tumors and how this proposed approach is expected to compare to brachytherapy with respect to efficacy. He also asked Dr. Morris to comment more about possible effects on the renal tubules. Dr. Johnson also raised a concern about the potential for hypothyroidism with this approach. Specifically, he questioned how well the risk was portrayed in the consent form and whether the risk of needing lifelong thyroid replacement hormone therapy was adequately addressed. The consent document includes a lengthy discussion about the collection of blood

samples for other research purposes, but the risks associated with such research are not adequately addressed. Dr. Johnson suggested that a separate consent document be developed for this aspect of the research.

Before beginning her analysis of the protocol, Dr. Carrasco reported that her lab identified and cloned the gene that codes for the NIS protein and that Albert Einstein College of Medicine filed a patent that was issued in May 2002. Dr. Carrasco further explained that she has no commercial relationships with respect to this patent. She pointed out that the non-technical abstract contained some inaccuracies and that the informed consent document needed a fuller discussion. She suggested the investigators consider the feasibility of administering inhibitors of thyroidal iodide organification in the thyroid, such as methyl imidazole (MMI), which might improve protection of the thyroid from radioiodide, and that the use of a low iodine diet to increase the specific activity of therapeutic radioiodine should be considered. She asked for an elaboration of how the dosages in rats were extrapolated to determine human dosages. She noted that the NIS could not differentiate between radioactive and cold iodine and that without thyrotropin (TSH) the NIS will not be expressed in the thyroid. Cell culture studies have shown that the NIS has a long half-life of the NIS protein. Therefore since eight days of suppressive therapy with levothyroxine may not be sufficient to provide optimal protection of the thyroid gland, longer pre-treatment suppressive therapy should be considered.

Dr. Ladenson raised questions about the risk of hypothyroidism, and the risk of thyrotoxicosis associated with T3 therapy. He also asked about how the measurement of tracer activity during the dosimetry part of the protocol and treatment dose would be ensured. He indicated that the investigators had addressed the comments and concerns raised during the preliminary review by reflecting the risks of hypothyroidism in the consent document. He noted that hypothyroidism easily diagnosed and treated, and that it is a risk in cancer treatment. Though a remote risk, the T3 therapy for TSH suppression could cause adverse cardiac events. Dr. Ladenson suggested safeguards be put in place to ensure cardiac monitoring and that individuals with known heart disease should be excluded. With regard to concerns raised about distortion of the reading of radioiodine activity in the prostate given its clearance through urine and stool, Dr. Ladenson noted that the investigators had explained the measures that would be taken to ensure the accuracy of the assay.

C. RAC Discussion

Other concerns raised by RAC members are as follows:

Ms. Kwan asked why the earlier enrollees, who receive the lower doses, might actually have a higher risk of hypothyroidism. She felt that this should be explained highlighted in the risks section of the informed consent document.

Ms. Levi-Pearl suggested that information about the financial conflict of interests of the investigators should be included in the informed consent document.

Dr. Anne Pilaro, FDA, noted that one would expect to see some immune cell infiltrates in the prostate following adenovirus administration.

Dr. Ladenson suggested that antithyroid drugs such as methimazole or propylthiouracil may have minimal additional benefit in TSH suppression and may increase the risk of adverse reactions.

Ms. King pointed out that the informed consent document does not make clear that the treatment is experimental. In addition, explanations are missing of the dose escalation portion of the study and the possibility (although low) that a research participant without sufficient uptake of NIS would not be eligible to receive radioiodine.

Dr. DeLuca asked whether the investigators expected to see extensive distribution of Ad throughout the tumor mass as was seen in preclinical models.

D. Investigator Response

In response to concerns about potential renal toxicity, Dr. Morris explained that though while the NIS gene is normally expressed in renal tubules, no adverse effects on renal function or any histological changes were seen in the animal models nor in patients treated for thyroid cancer. Because the expression of NIS in the kidney is low level, toxic effects on the kidney are not anticipated.

Regarding how well the approach proposed in the protocol compares to brachytherapy, Dr. Morris suggested that the proposed approach may be more effective because the diffusion of the virus may yield better distribution of the radioiodine effect.

In response to concerns about the potential for hypothyroidism and a question about extrapolation of animal doses, the investigators indicated that they had reevaluated the planned dose of radioiodine. If the NIS gene uptake in the prostate is significant, they should be able to use lower doses of radioiodine that would reduce the risk of hypothyroidism. Participants who receive less NIS gene or who had lower expression may have a higher risk of hypothyroidism because a higher dose of radioiodine will be needed. The highest dose of 200 millicuries does carry a risk of hypothyroidism (as high as 50% percent) and that this will be explained in the consent.

With respect to the portions of the informed consent document devoted to sample collection in this study, Dr. Morris explained that those were derived from both institutional requirements as well as State of Minnesota requirements. The points raised by the RAC were well taken and will give Dr. Morris an opportunity to discuss the consent form language with the institutional IRB.

With respect to handling of sample collection in the informed consent document, Dr. Morris explained that the language reflects institutional as well as State of Minnesota requirements. Dr. Morris agreed to discuss the RACS concerns with the IRB.

With respect to assaying for host immune response in the prostate, Dr. Morris noted that they are currently studying this issue in animal models. They are looking for both adverse events as well as possible antitumor effects.

With regard to the distribution of the virus in the prostate, Dr. Morris explained that direct ultrasound imaging should help improve uniform distribution in the prostate.

Dr. Morris was open to making all of the changes suggested to the informed consent document.

Dr. Morris explained why they decided not to use methimazole or propylthiouracil, but indicated that they will reconsider the decision.

With respect to the timing of T3 suppressive therapy, Dr. Morris agreed that, because the half-life of NIS is long, it might be beneficial to increase the duration of T3 suppressive therapy, and that they will consider increasing it to the suggested 14 days.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Friedmann summarized the RAC recommendations, suggestions, and comments as follows:

- To further reduce the risk to the thyroid due to the administration of radioiodine, TSH should be suppressed with T3 supplementation for at least 8 days prior to the administration of the investigational agent since the half-life of the sodium iodide symporter (NIS) (as shown in rats) is 5 days and TSH is required for the NIS to work in the thyroid.

- Even though adverse cardiac effects of radioactive iodine would be rare in the usual situations of administration, patients with known cardiac disease should be excluded from participation in this Phase I study to increase research participant safety

- The informed consent document should be modified as follows:
    - The number of research participants to be enrolled should be clarified in the protocol and stated in the informed consent document.
    - The dose escalation study design should be described in lay language. Ms. King provided an example of such wording at the RAC meeting and OBA can provide this example if needed.
    - Because it may be counterintuitive, an explanation is needed about why research participants who receive a lower dose of the NIS-containing adenoviral vector may be at a higher risk for developing the side effect of hypothyroidism.
    - Clearly state that research participants who show no NIS uptake will not undergo further investigational treatments on this protocol.
    - The name of the anesthesia to be used in the study should be the same as it is in the protocol and the risks of anesthesia should be discussed.
    - The contraception requirements, both the type and duration, should be clearly stated.
    - The value of a separate informed consent document for the research use of tissues should be discussed with the IRB.
    - The request for permission for an autopsy should be moved to a separate section.
    - Potential or real financial interests the investigators have in this protocol should be disclosed.

G. Committee Motion 6

It was moved by Dr. Gelehrter and seconded by Dr. Wara that these recommendations expressed the comments and concerns of the RAC. The vote was 13 in favor.

XII. Data Management Report/Drs. Simari and Wara

Dr. Simari reported that 18 gene transfer protocols were submitted to the OBA in the past reporting quarter (February 2002 to May 2002), 6 of which were selected for public RAC review at this meeting. A total of 156 serious adverse events (SAEs) were reported to the OBA, of which 113 were initial reports and 43 were followup reports. Twelve were listed as Category A, which is the category for serious, unexpected, and potentially associated AEs. Dr. Simari discussed three protocols briefly because of the nature of the AEs.

Protocol #322 is a Phase I study of *ex vivo* gene transfer for Alzheimer's disease. In this study, a research participant sustained a cortical hemorrhage during the surgical procedure to implant the gene transfer product. This event was associated with superficial vessel bleeding that subsequently involved the cortex following product delivery. The research participant developed medical complications secondary to this event, including immobility, myocardial infarction, and cardiac arrest and following a prolonged period of hospitalization, the research participant died. In response to this event, the investigators made five changes to the protocol to avoid future problems. Dr. Wara elaborated upon these changes later in the discussion.

Protocol #388 is a double-blind, randomized, placebo-controlled, dose-ranging, 26-week study to assess the safety and efficacy of Ad vascular endothelial growth factor 121 (Ad/VEGF121) in peripheral artery disease. Two months after receiving the Ad/VEGF121, a participant experienced renal insufficiency and ascites. Cytology reports of the ascitic fluid showed presence of an adenocarcinoma, and an upper gastrointestinal (GI) exam showed adhesions believed to be due to intra-abdominal carcinomatosis. The research participant's course was complicated by associated morbidities of renal dysfunction that were speculated to be due to concomitant use of nonsteroidal anti-inflammatory drugs as well as severe left ventricular dysfunction and stroke. The primary source of the adenocarcinoma remains uncertain.

Protocol #481 is an open-label, Phase IB/II study of the safety, tolerability, and efficacy of G207, a genetically engineered, type 1 HSV administered intracerebrally to research participants with recurrent malignant glioma. This report is a followup report of an SAE previously discussed at the March 2002 RAC meeting, which involved a research participant who had a seizure 72 hours after surgery. The investigator's followup report suggested that there had been minor improvements in the leg and upper extremity functions, but the neurologic deficits were still present and exceeded the individual's status prior to the event. A second followup report stated that the individual subsequently died. The autopsy showed multiple sites of metastatic tumors throughout the brain, and the PI suggested that the cause of death was likely due extensive progression of the disease. A second participant in that study developed deterioration of mental status following delivery of the study product. However, with intensive care unit treatment and steroid therapy, the individual's neurologic status returned to baseline, and the individual continues to do well. The PI deemed this second event possibly related to the gene transfer agent.

Dr. Wara reported that 51 protocol amendments were submitted to the OBA, the majority of which were related to adding a new clinical site or a new investigator and minor modifications of exclusion and inclusion criteria. One amendment was discussed—Protocol #322, a study to determine a possible Alzheimer's disease treatment—in which an unexpected SAE (discussed above) was deemed unrelated to the study agent but related to the surgery necessary for the injection of gene transfer agent. Investigators made several significant changes to the protocol as a result of this event and modified the informed consent document. If another unexpected intraoperative event occurs, a neurosurgeon unassociated with the trial will be consulted regarding the advisability of continuing with cell implants intraoperatively.

Dr. Wara reminded RAC members of an amendment to the NIH Guidelines that allow PIs to submit annual reports to the NIH/OBA at the same time as they submit their annual reports to the FDA. As a result of this new requirement, an increase in the number of annual reports is anticipated. Harmonization of the reporting requirements is expected to increase compliance with both the annual and expedited reporting.

XIII. Discussion of Human Gene Transfer Protocol #0201-534: Phase I Study of Ad4-ΔE3-HIV$_{env}$ and Ad4-ΔE3-HIV$_{gag/pro}$ Recombinant Vaccines in HIV-Negative Volunteers

Principal Investigator:	Mark Connors, M.D., National Institute of Allergy and Infectious Diseases
Sponsor:	None
RAC Reviewers:	Dr. Breakefield, Ms. King, Dr. Linial, and Dr. Wara
Ad Hoc Reviewers:	Stephen Dewhurst, Ph.D., University of Rochester, and Ira J. Fox, M.D., University of Nebraska Medical Center

Dr. Rose noted that the review of this protocol is a special circumstance because the NIAID is seeking the RAC's advice about how to ensure the highest level of safety for research participants. Intramural investigators at the NCI are collaborating in this protocol.

A. Protocol Summary

This Phase, I double-blind, randomized, dose-escalation study is designed to study the safety and immunogenicity of live, recombinant E3-deleted Ad type 4-HIV-1$_{MN}$ vaccines carrying HIV-1 *env* plus *rev* or *gag/protease* plus *rev* inserted genes in human immunodeficiency virus (HIV)-negative volunteers. Intranasal and oral administration of the vaccines will be assessed separately, initially in volunteers who have antibodies to adenovirus (Ad-seropositive). Once safety is established in these individuals, testing of an equal or lesser dose will proceed in volunteers who do not have antibodies to adenovirus (Ad-seronegative.

The primary goals of the study are to evaluate the safety of the Ad4-ΔE3-HIV$_{env}$ and Ad4-ΔE3-HIV$_{gag/pro}$ vaccines following oral or intranasal administration and assess humoral, cellular, and mucosal immune responses against both the vector and the inserted genes. The Ad4-ΔE3-HIV$_{env}$ will be evaluated first at

up to three dose levels. Once safety is established at the initial dose, a second and third round of testing will be conducted each at the next tenfold higher dose. Control subjects will receive an intranasal or oral placebo. Each dose level of Ad4-ΔE3-HIV_{env} will be assessed in three volunteers for each route of administration (oral or intranasal), and a placebo will be administered to one volunteer for each route at each dose level. In this phase of the study, up to 30 Ad-seropositive and 30 Ad-seronegative individuals (allowing for dropouts) will be enrolled to fully evaluate safety and immunogenicity in the first part of the protocol.

Subsequently, the Ad4-ΔE3-$HIV_{gag/pro}$ vaccine will be assessed in three Ad-seropositive and three Ad-seronegative volunteers, by both the oral and intranasal routes, at the safe doses established for the Ad4-ΔE3-HIV_{env} vaccine. One additional volunteer in each immunization group will receive a placebo, orally or intranasally as appropriate. Once the safety of both vaccines is established, up to 10 additional Ad-seronegative volunteers may be added at the established safe oral dose and 10 at the established safe intranasal dose to more fully evaluate the immunogenicity of the two recombinant vaccines administered in combination, thus at two times the established dose. Therefore, up to 50 volunteers may be enrolled for the second part of this protocol.

All research participants will be followed for 8 weeks following immunization and again at 52 weeks to evaluate any long-term toxicity.

B. Reviews by RAC Members and Ad Hoc Reviewers

Ms. King, and Drs. Breakefield, Linial and Wara submitted written reviews, as did the *ad hoc* reviewers, Drs. Dewhurst and Fox, to which the investigator responded in writing and during this meeting.

Dr. Breakefield focused on the vector, toxicity, and the informed consent document. She asked about the selection of the Ad4 serotype for the vector, and the plans for monitoring vector shedding including evaluation of possible transmission to contacts. She suggested using quantitative PCR to monitor vector shedding. Regarding toxicity, Dr. Breakefield asked about preclinical studies to evaluate potential toxicity to the lung and GI tract, and what was the possibility that vector latent in lymphoid tissues could migrate throughout the body, and end up in the brain or other tissues. She suggested that intimate contacts of the research participants be consented.

In order to better calculate the harm/benefit ratio for normal volunteers and contacts possibly exposed by horizontal transmission, Ms. King asked for more information about the rationale for the use of a replication competent vector. Information on possible transmission of vaccine to individuals in close contact with research participants should be expanded in the informed consent documents for both the research participants and the contacts. Because participants may be in isolation for an indefinite amount of time during viral shedding, the informed consent document should be clearer about the potential length of the quarantine period and about what would happen if a participant chose to drop out off the study during this period. Ms. King also provided specific suggestions for the informed consent document concerning genetic and specimen storage, risks to participants, risks to others, long-term follow-up, request for autopsy, and possible benefits.

Dr. Linial requested preclinical data on the specific constructs to be used in this protocol, and more detail about the assays to measure the immune responses in the participants. She asked about the potential for the generation of virus-like particles (VLP) from the vector expressing gag/pro and whether this would be monitored in the participants and contacts. Because deletion of E3 from adenovirus increases viral pathogenicity, she recommended further study to determine the stability of the transgene inserted into the E3 region. She asked whether potential research participants with minors living in the household would be excluded from participation in this study.

Dr. Wara also requested more information about any preclinical data in a large-animal model evaluating this specific vector and gene insertion. She also expressed concern about transmission of Ad4 to household contacts. While her preliminary questions about immunogenicity were addressed, she also wanted to know how the investigators would assess the mucosal immune response.

Dr. Dewhurst noted the potential for spread of the replicating Ad vaccine in the general population and asked for evidence that the vector is attenuated for pathogenicity and transmission. He requested more information on the immunological analyses planned, in particular how possible viral persistence would be examined. He asked why only the participants receiving the vaccine intranasally are to be isolated and not those receiving the oral dose. Dr. Dewhurst requested more information about the nasal AccuSpray device that will be used for intranasal immunization. He also suggested that the stability of the transgene insert in the E3 deletion should be assessed in participants and contacts and information about the increased pathogenicity of E3 deleted adenovirus should be included in the informed consent document. He asked whether the investigators planned to compare the proposed vaccine to an E1 deleted replication incompetent Ad4 vector.

Dr. Fox stated that it was difficult to determine how the data provided from previous animal and human studies directly related to this proposal. He requested more information about the proposed analysis of the immune response, including assays for neutralizing antibodies and cytotoxic T lymphocytes. Because infected cells have been documented as persisting in the lymphoid system for up to 2 years, Dr. Fox wondered whether some research participants could shed virus for that long, and whether late infection of contacts would be possible. Because of the concerns about the use of a replication-competent vector, Dr. Fox asked whether it would be possible to determine from the data resulting from this protocol whether the replication competent vector is more effective as an immunogen than a replication-incompetent vector.

C. RAC Discussion

Other concerns raised by RAC members included the following:

- Dr. Linial requested a synopsis of the sensitivity of the shell vial bioassay.
- Dr. Dewhurst requested clarification about why research participants who receive the nasal inoculation would be housed in isolation in the NIH Clinical Center until shedding had ceased.
- Dr. Gooding asked whether immunization with the Ad4 vaccine might cause research participants and their intimate contacts to test positive on HIV tests.
- Dr. DeLuca reiterated the importance of fully informing anyone coming in contact with the research participants especially since unknowing recipients of the vaccine may test positive on future HIV tests.
- Dr. Gooding asked about the size of the vaccine construct genome compared with the wild type and whether any change in size could affect vector replication or stability.
- Dr. Gooding asked about the rationale for starting this protocol with intranasal inoculations rather than with oral immunization using enteric-coated capsules, which have been shown to be safe.
- Dr. Friedmann asked whether the vaccine preparation would contain VLPs and, if so, could there be an immune response to the VLPs that would confound the analysis of the vaccine immunogenicity.
- Dr. Breakefield wished the PI to be particularly vigilant about finding tropism changes resulting from this hybrid virus.
- Dr. L. Johnson asked how long participants at the higher doses receiving nasal injection would be isolated.

D. Investigator Response

Dr. Connors reiterated the safety of the intranasal spray proposed for this protocol by citing the significant experience with an Ad vaccine in Ad-seropositive individuals in the military and other studies. Based on other studies and the understanding of the behavior of Ad4 virus, he indicated that Ad-seronegative individuals should not be at risk for disease that is any more virulent than that caused by wild-type Ad. Research participants may develop a sore throat or a fever, but they will be monitored daily, especially for signs of lower respiratory tract infection.

Regarding the shell vial bioassay, Dr. Connors explained that it involves centrifuging a clinical specimen onto a slide and then detecting virus by immunofluorescence.

Dr. Connors agreed with Dr. Linial's and Dr. Dewhurst's suggestion that the investigators assay the stability of the vaccine to determine whether the transgene insert becomes deleted from the E3 region.

In response to the question of whether participants and contacts will test positive for HIV, Dr. Connors responded that it was possible on an enzyme-linked immunosorbent assay (ELISA) test but not the Western blot test. He explained that the Western blot test detects responses to a variety of different gene products. Research participants will be immunized with a single gene product, so it will be possible to distinguish a recipient of the Ad4 vaccine from someone who has been infected with HIV. In responding to her question about the size of the vaccine construct, Dr. Connors responded that it is approximately the same size as the wild type genome and the vaccine has been stably passaged *in vitro* for almost ten years.

Dr. Connors expected that the informed consent documents would be undergoing further revision and they would consider the suggestions of the RAC members regarding how to inform both the research participants and their contacts about the possibility of inadvertent transmission of the vaccine. The investigators are considering consenting other people in the household, enrolling them as research participants, and following them serologically regarding Ad4 and HIV. Potential participants with minors in the household will be excluded from this protocol.

In answer to the question regarding the isolation period for nasal injection participants, Dr. Connors indicated that the isolation period would be 1 to 2 weeks based on other studies of Ad-seropositive individuals given an intranasal inoculation.

In response to the concern about the vaccine preparation containing VLPs, Dr. Connors explained that the vaccine undergoes a purification step that should exclude most VLPs. Concentration of VLPs in the vaccine should be extremely low.

Dr. Guroff addressed the question about the study of mucosal immunity by explaining that an analysis of overall immunogenicity including levels of mucosal IgA and IgG directed against the vaccine is planned. If a strong immune response is detected, additional assays including vaginal or rectal biopsies may be added.

Regarding the isolation of nasal inoculation recipients, Dr. Connors explained that a considerable number of data on intranasal administration indicate that such administration is safe but that investigators want to be particularly conservative. Thus, seropositive research participants will be required to stay at the NIH Clinical Center until the virus is no longer being shed. Accrual to such a clinical trial will be difficult, as it might require participants to be isolated for up to 1 month. Regarding those research participants who receive the enteric vaccine, Dr. Connors stated that they will be sent home with instructions to avoid intimate contact with others.

Dr. Connors explained that the data and safety monitoring board (DSMB) would evaluate the results from each group before allowing the trial to move to the next step. The safety and immunogenicity data from the Ad-seropositive research participants will inform the decision about whether or not to proceed to intranasal administration to Ad-seronegative individuals.

Dr. Chanock, who developed Ad4 and Ad7 vaccines used by the military, summarized some of those data. Ten million military recruits were vaccinated with the Ad4 vaccine, 66 percent of those were Ad-seronegative. No adverse events were seen in the follow-up by the U.S. Army. Extensive safety information exists for about 1 million individuals who received the enteric-coated Ad4 vaccine. In the military Ad4 vaccine studies, vaccinated and unvaccinated recruits were housed in the same barracks, but no cases of transmission from vaccinated to unvaccinated individuals were observed. Intimate contact appears to be necessary for transmission of the enteric vaccine.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Friedmann summarized the RAC recommendations, suggestions, and comments as follows:

- Consider a combination of both infectious Ad4 assays and quantitative PCR assays to monitor viral shedding in the research participants, especially those receiving the vaccine via the nasal route. This may provide valuable additional information with respect to the consequences of nasal vaccine administration.

- Because of the increased pathogenicity observed with ΔE3 adenovirus compared to wild type adenovirus, further studies are needed of the stability of the transgene insert in the vaccine. A PCR based assay should be used to examine the stability of the insert in tissue culture. During the clinical study, vector shed in respiratory secretions and stool should be screened for loss of the transgene. A competition assay should also be developed to compare replication of the ΔE3 vector with and without the transgene insert to determine whether ΔE3 vector with the transgene deleted would outgrow the vaccine.

- Given its extensive experience, the NIH Bioethics Center may be an especially useful source of advice during the development of the informed consent documents for clinical trials related to HIV.

- The informed consent documents should more clearly explain the rationale for the potentially lengthy isolation period for research participants in the intranasal installation arm. This is important so that potential research participants understand the importance of isolation, what to expect during the isolation period, and potential consequences, for themselves and for others, of dropping out of the study before the end of the isolation period.

- Regarding the possible transmission of vector to contacts, a clear explanation of the likelihood and nature of the risks of inadvertent infection should be provided in separate informed consent documents customized for research participants or contacts. The research participants should be provided with more information about how to avoid putting contacts at risk (e.g., the control guidelines recommended for Ad4 infections that cause conjunctivitis and acute febrile respiratory disease described in the American Public Health Association's *Control of Communicable Diseases in Man*) and restricting intimate contact with others both in and out of the household for the duration of active viral shedding (i.e., during the period when active virus can be isolated from bodily fluids, secretions or substances as well as during the immediate four-week period following virus administration). Participants should be provided educational materials they can share with close contacts about the risks to others and the symptoms of infection that would indicate a need to test for inadvertent vaccination and infection.
- Because of concerns about possible transmission of vaccine virus to household contacts, contacts should be tested periodically for the presence of Ad4-specific and HIV-specific humoral immune responses. This should occur at baseline, at the termination of the study and at one additional interim time point to be determined by the investigators.

G. Committee Motion 7

It was moved by Dr. Breakefield and seconded by Dr. L. Johnson that these recommendations expressed the comments and concerns of the RAC. The vote was nine in favor.

XIV. Closing Remarks

Dr. Friedmann thanked the RAC members and the audience and members of the public. He reminded RAC members that this was the last RAC meeting for Dr. Breakefield, Ms. King, and Ms. Levi-Pearl.

XV. Adjournment/Dr. Rose

The meeting was adjourned by Dr. Rose at 3:40 p.m. on June 21, 2002.

[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.]

…/s/…

Stephen M. Rose, Ph.D.
Executive Secretary

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

Date: …/s/…

Theodore Friedmann, M.D.
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Attachment I
Committee Roster

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Attachment II
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Attachment III
Abbreviations and Acronyms

Ad	adenovirus
AdiNOS	adenovirus carrying the inducible nitric oxide synthase gene
AE	adverse event
AV	arteriovenous
BSL	biosafety level
CEA	carcinoembryonic antigen
DNA	deoxyribonucleic acid
DTH	delayed-type hypersensitivity
DSMB	data and safety monitoring board
ED	erectile dysfunction
ELISA	enzyme-linked immunosorbent assay
FDA	U.S. Food and Drug Administration
GeMCRIS	Genetic Modification Clinical Research Information System
GI	gastrointestinal
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IBC	institutional biosafety committee
iNOS	inducible nitric oxide synthase
IRB	institutional review board
MTD	maximum tolerable dose
MV	measles virus
MV-CEA	measles virus expressing carcinoembryonic antigen
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NIS	sodium iodide symporter
OBA	Office of Biotechnology Activities (formerly ORDA, Office of Recombinant DNA Activities)
OD	Office of the Director, National Institutes of Health
PI	principal investigator
p/kg	particles per kilogram
PTFE	polytetrafluoroethylene
RAC	Recombinant DNA Advisory Committee
VLP	virus-like particle