RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 3 - 4, 2003

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

CONTENTS

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

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

December 3-4, 2003

The Recombinant DNA Advisory Committee (RAC) was convened for its 94th meeting at 9:00 a.m. on December 3, 2003, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Theodore Friedmann, RAC Chair, presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. until 4:45 p.m. on December 3 and from 8:30 a.m. until 2:50 p.m. on December 4. The following individuals were present for all or part of the meeting.

Committee Members

W. Emmett Barkley, Howard Hughes Medical Institute
Martha C. Bohn, Northwestern University Medical School
James F. Childress, University of Virginia
Neal A. DeLuca, University of Pittsburgh
David L. DeMets, University of Wisconsin Medical School
Theodore Friedmann, University of California, San Diego
Thomas D. Gelehrter, University of Michigan Medical School
Larry G. Johnson, University of North Carolina, Chapel Hill
Philip R. Johnson, Jr., Columbus Children's Hospital
Terry Kwan, TK Associates
Maxine L. Linial, Fred Hutchinson Cancer Research Center
Bernard Lo, University of California, San Francisco
Madison Powers, Georgetown University
David Sidransky, Johns Hopkins University School of Medicine
Robert D. Simari, Mayo Clinic and Foundation
Diane W. Wara, University of California, San Francisco

RAC Executive Secretary

Stephen M. Rose, Office of the Director (OD), National Institutes of Health (NIH)

***Ad Hoc* Reviewers/Speakers**

Donald L. Budenz, M.D., Bascom Palmer Eye Institute
Shawn M. Burgess, Ph.D., National Human Genome Research Institute (NHGRI), NIH
Nancy M.P. King, J.D., University of North Carolina, Chapel Hill
Sue L. Levi-Pearl, Tourette's Syndrome Association, Inc.
Cheryl L. McDonald, M.D., Office of Biotechnology Activities (OBA), NIH
Evan Y. Snyder, M.D., Ph.D., The Burnham Institute *(via teleconference)*

NIH Staff Members

Sussan Eftekhari, OD
Robert Jambou, OD
Laurie Lewallen, OD
Harry L. Malech, National Institute of Allergy and Infectious Diseases, NIH
Maureen Montgomery, 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.

Marina O'Reilly, OD
Jennifer M. Puck, NHGRI, NIH
Alexander Rakowsky, OD
Gene Rosenthal, OD
Thomas Shih, OD
Allan Shipp, OD
Gisele White, OD

Others

There were 87 attendees at this 2-day RAC meeting. A full list of RAC members, *ad hoc* reviewers and speakers, and nonvoting and agency liaison representatives is included as Attachment I. A list of public attendees is included as Attachment II.

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

Dr. Friedmann, RAC Chair, called the meeting to order at 9:00 a.m. on December 3, 2003. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on November 12, 2003 (68 FR 64113). Issues discussed by the RAC at this meeting included public review and discussion of three protocols, a data management report, update on the RAC Gene Transfer Clinical Trial Design Working Group, update on development of a mechanism to apprise the RAC of investigator and institutional responses to RAC reviews, amendments and updates to a gene transfer protocol first reviewed in December 2000, an educational seminar on global site preferences for proviral integration in the human genome, and presentation of the final NIH guidance document on informed consent for gene transfer research from the RAC's Informed Consent Working Group.

Dr. Rose reminded RAC members of the rules of conduct that apply to them as special Federal Government employees.

Dr. Rose informed the RAC that Baruch A. Brody, Ph.D., Baylor College of Medicine, has resigned his appointment on the RAC for personal reasons, and the OBA is in the process of identifying a replacement.

II. Minutes of the September 17, 2003, RAC Meeting/Drs. Gelehrter and P. Johnson

Drs. Gelehrter and P. Johnson noted that, with the exception of a few minor typographical changes and one minor clarification, no other changes were required to the minutes of the September 17, 2003, RAC meeting.

A. Committee Motion 1

It was moved by Dr. Wara and seconded by Dr. Powers that the RAC approve the September 17, 2003, RAC meeting minutes. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Update on the RAC Gene Transfer Clinical Trial Design Working Group/Dr. DeMets and Dr. McDonald

Dr. DeMets reported that this working group had made no progress since the previous RAC meeting. This working group was born out of a series of discussions about appropriate trial designs for some of the clinical trials being reviewed by the RAC and what the sample sizes should be. This working group will provide recommendations, for the RAC and for the NIH in general, for investigators to use as a guide.

The working group consists of Ms. King; Dr. Lo; Susan Ellenberg, U.S. Food and Drug Administration (FDA); Jim Wheaton, a statistician involved with AIDS trials; Dr. McDonald; and Dr. DeMets. Dr. DeMets recently asked Dave Harrington, a senior statistician at the Dana-Farber Cancer Institute, to join the working group to lend his expertise as a statistician who is familiar with cancer trials.

Potential topics to be explored include the basic design, how many subjects should be included, which designs should be used, which subjects should be used first in the early-phase trials, which end points should be used, which surrogate end points would be useful at various stages of investigation, and which animal studies should be used to increase certainty about the appropriateness of proceeding to the next phase of research.

A conference call among working group members has already occurred, the group met for lunch on Day Two of this RAC meeting, and a face-to-face meeting is likely in late January or early February 2004.

Dr. Rose noted that one possible result of this working group would be a guidance document similar to that crafted by the RAC's Informed Consent Working Group. RAC members and OBA and FDA staff members were invited to provide feedback and advice to the Gene Transfer Clinical Trial Design Working Group.

IV. Data Management Report/Drs. L. Johnson, Simari, and Wara

Dr. Simari reported that there had been 14 protocol submissions since September 2003, 13 of which were not selected for public review. Protocol #610 was submitted after the September 2003 RAC meeting, and two other protocols (#589 and #592) had been deferred from the September 2003 RAC meeting. Of the 13 trials not selected for public review, 10 were for cancer, 2 were for cardiovascular disease, and 1 was for infectious diseases.

The OBA tabulated data and provided background information on adverse events (AEs) during the past 3 months: A total of 141 AEs were reported, 139 of which were considered serious (92 initial reports and 47 followups). A total of 21 were classified as "A" events; 10 of these were initial reports, and 11 were followups. Dr. Simari summarized two of the serious AEs:

- Protocol #453 is a multicenter, open-label, two-part, dose-escalation study to determine the tolerability of interferon-β gene transfer in the treatment of recurrent or progressive glioblastoma multiforme. One participant experienced mental status changes 1 week after the study agent was administered and subsequently developed seizures; on August 30, 2003, this individual died, and an autopsy was performed. The pathologist concluded that high levels of viral vector were present in the tumor bed and that these levels of vector may have persisted and directly caused the leptomeningeal necrosis and small-vessel necrosis and thrombosis that led to the participant's multifocal hemorrhagic infarctions. DNA polymerase chain reaction (PCR) results are pending, and the autopsy is continuing to be performed; however, on the basis of this concern, the sponsor (Biogen) has put this study on hold. Dr. Simari stated that, until final data are submitted, it should be assumed that this incident was due to expression of the transgene; he also noted that the FDA is looking into other studies that use a similar vector for this particular indication.

- Protocol #544 is a Phase I study to evaluate the safety and pharmacokinetics of pro-1, a liposome-encapsulated thymidine kinase gene formulation in patients with stage IV metastatic melanoma. AEs occurred in the first two participants: Four to ten hours after completion of intravenous (IV) delivery of .03 milligrams per kilogram of the DNA study product, these two individuals developed chills, rigors, tachycardia, tachypnea, fever, hypotension, and decreased oxygen saturation. They were treated with Demerol, acetaminophen, hydrocortisone, supplemental oxygen, and IV normal saline and were admitted to the hospital for observation. Their symptoms resolved by the next morning. It was noted in the letter from the sponsor (Protiva) that these two events suggest that the doses administered to these participants are above the no-effect level for humans, although well below that level for mice.

Dr. Wara reported that 52 annual updates had been filed in the past 3 months: Ten included a change in investigator or site, 7 were study closures, and 35 were protocol amendments. She briefly discussed the amendments reported from six protocols:

- Protocol #371 is a Phase I safety study in patients with severe hemophilia B using adeno-associated viral vector to deliver the gene for human Factor IX into the liver. At the December 2001 RAC meeting, RAC members discussed the finding of adeno-associated virus (AAV) in the semen of the first study participant. The protocol was revised at that time to address FDA and RAC comments, and the investigators agreed to obtain semen samples monthly until three serial samples of motile sperm tested negative by DNA PCR. In addition, 60 days was to elapse between the last individual enrolled at a given dose and the semen motile sperm fraction negative for vector sequences before the first individual at the next dose level was to be treated. Because of technical difficulties, the current amendment addresses analyzing whole semen samples rather than motile sperm fraction. The time lapse between cohorts has been decreased from 60 days to at least 4 weeks.

- Protocol #467 is a trial using vascular endothelial growth factor (VEGF) gene transfer for diabetic neuropathy. The principal investigator (PI) and the sponsor proposed broadening the exclusion criteria from "have any evidence of history of neoplasm" to "have any history of neoplasm within the past 5 years." The PI supports this change by stating that there is no evidence that VEGF-165 has induced or expedited the growth of any neoplasm in any of the 102 participants enrolled in the two protocols utilizing this transgene in the United States or in the approximately 900 individuals treated worldwide with various angiogenic growth factors. The RAC members who reviewed the protocol revisions suggested a discussion of a systematic assessment for neoplasm of participants who have received growth factor worldwide, rather than just a statement to that effect. Additional discussion centered on whether the 5-year window was conservative enough for accrual in this study, especially since some neoplasms—for example, breast cancer—do not recur within the proposed 5-year window.

- Protocol #516, a study of *ex vivo* retroviral gene transfer of X-linked severe combined immunodeficiency disease (X-SCID), will use gene transfer only in research participants who failed all other treatments, including bone marrow transplant. The OBA was notified of a request by the PIs to remove this protocol from clinical hold. The proposed first participant is an 11-year-old boy who has a mutation in the interleukin-2 (IL-2) RG gene that allows for the expression of a normal common chain protein in a trace amount; that trace amount has allowed this boy to survive to 11 years of age. The participant's age suggests less risk from gene transfer; however, this 11-year-old boy's trace amounts of normal IL-2 common chain protein likely will result in the loss or diminution of a selective advantage for the transduced CD34 cells. Although the benefit is perhaps less, the risk from participation is less as well. Investigators Dr. Malech and Dr. Puck noted that both they and the boy's family agree that this should be tried, despite the fact that the likelihood of success is less than in the infants who are treated. Dr. Puck described the situation and conditions of three other individuals between the ages of 7 and 12 years.

- Protocol #452 is a multicenter, randomized, double-blind, placebo-controlled, Phase IIb/III study to evaluate the efficacy and safety of Ad5 FGF-4 in patients with stable angina; a total of 273 participants have been enrolled, and 131 serious adverse events (SAEs) have been reported. For the number of participants enrolled, most of whom had advanced disease at the time of gene transfer, the nature of the SAEs is reassuring because there are very few unexpected or possibly related AEs.

- Protocol #487 is an open-label, Phase I, single-administration, dose-escalation study of adenovirus pigment epithelium-derived factor in neovascular age-related macular degeneration. Seventeen participants have been enrolled, with 13 followed for at least 12 weeks postinjection. Only one SAE has been reported—a recurrence of bladder cancer in a participant enrolled in the first cohort. Neutralizing antibody results are complete for 12 of these participants, and only 1 of the 12 had a substantial rise in neutralizing antibody—week 3 postinjection with a return to baseline by week 12. These AE data are reassuring.

- Protocol #594 is a Phase I study to determine the safety and biological activity of cell-mediated gene transfer using transgene C in participants with degenerative joint disease of the knee prior to total knee arthroplasty. The OBA received a letter from the chair of the institutional review board (IRB) at Sinai Hospital in Baltimore stating that the IRB would review this study only after the recommendations of the RAC had been addressed.

V. Update on the Development of a Mechanism to Apprise the RAC of Investigator and Institutional Responses to RAC Reviews/Dr. McDonald and Dr. Thomas Shih, OBA Staff

At the June 2003 RAC meeting, a proposal was brought forth to develop a mechanism to provide feedback to the RAC regarding its recommendations to sponsors and investigators. Dr. McDonald reviewed the procedure and timetable for the RAC review process: The PI receiving a letter from the RAC triggers completion of the RAC review process; after the PI receives that letter, the sponsor and the investigators are supposed to pursue institutional biosafety committee (IBC) and IRB approvals.

With respect to outreach efforts to IRBs and IBCs, the OBA's Director of Outreach, Mr. Allan Shipp, hosted the February 2003 meeting in San Diego "The Future Face of IBCs: Evolving Worlds and Responsibilities: Upcoming Challenges and Opportunities." In April 2003 Mr. Shipp participated in a medical research summit with clinical research administrators in Washington, D.C.; also in April 2003 he presented at the annual meeting of the Association of Clinical Research Professionals. In October 2003 Mr. Shipp, as well as Dr. Rose and Dr. Rosenthal of the OBA, presented at the annual meeting of the American Biological Safety Association, the professional organization for biosafety officers. In December 2003 Mr. Shipp gave five presentations at the annual meeting of the Applied Research Ethics National Association and Public Responsibility in Medicine and Research (PRIM&R), both of which are organizations for IRB professionals and others associated with clinical research. Dr. McDonald noted that the OBA is ready, willing, and able to work with institutional committees and to welcome their feedback, questions, and comments—bringing those to the RAC for discussion as appropriate. On the OBA Web site, there is a page dedicated to issues pertinent to IBCs.

A. RAC Discussion

Dr. Rose asked the RAC members to look at some of the letters sent to PIs after RAC review, concentrating on the section that specifically talks about the reporting requirements. Feedback is needed on alternative wording that would better clarify that this is the end point of the RAC formal review process, that is, that the IBC can act at this point but the PI is still subject to the reporting requirements as set forth in Appendix M-I of the *NIH Guidelines*.

Dr. Friedmann stated that most IBCs do not fully understand the reporting mechanism and their prerogatives as a local committee. Despite all of the communication from the OBA to the IBCs, uncertainty and confusion remain.

At the suggestion of Ms. Kwan, Dr. McDonald agreed that the OBA would produce a quarterly chart to summarize the status of all protocols discussed by the RAC, with the acknowledgment that updates would be possible only from those PIs who have provided update reports to the OBA. This chart would include the protocols registered with the OBA in the current quarter, the ones chosen for public discussion, and a status report of each protocol at subsequent RAC meetings.

Several RAC members asked for clarification of the contents and timing of the "20-day letter," the letter that the PI must provide to the OBA within 20 working days of beginning to obtain informed consent from the first research participant. Dr. Lo suggested that a distillation of the formal responses contained in the 20-day letter be provided to all RAC members, not just the data management subgroup of the RAC; Dr. McDonald agreed.

Dr. L. Johnson pointed to the need to focus on improving the quality of proposed trials. He suggested selecting a few protocols on a quarterly basis and reviewing the responses received from the protocols that have RAC letters; then the RAC could point out what was done, what was not done, and whether for any reason a recommendation was considered useful or not useful. This process would serve the purpose of obtaining feedback on which RAC recommendations are useful, providing an informational process for the RAC and for the public about the recommendations, using the process for quality improvement purposes.

Additional RAC member input regarding the feedback process should be sent to Dr. McDonald, who will provide another brief update at the March 2004 RAC meeting.

VI. Amendments and Updates to Human Gene Transfer Protocol #0010-419: Intratumoral Injections of a Replication-Incompetent Adenoviral Vector Encoding a Factor VII Immunoconjugate to Induce a Cytolytic Immune Response Against Melanoma Tumors: A Pilot Trial

Principal Investigator: Albert B. Deisseroth, M.D., Ph.D., Sidney Kimmel Cancer Center

In-depth review and public discussion of this protocol occurred at the December 2000 RAC meeting. This discussion had been postponed from the September 2003 RAC meeting because of Hurricane Isabel.

Dr. Deisseroth stated that his interest in returning to the RAC was based on protocol revisions, site changes, changes in vector, and the opportunity to share interim progress in response to RAC concerns. This gene transfer protocol involves release of a protein into the systemic circulation following subcutaneous injection of the vector that carries the transcription unit.

Changes in this protocol since RAC review in December 2000 included the following:

- Preparation of a new vector due to quality-control problems in producing the proposed vector.
- Expanded inclusion criteria to individuals with diseases with subcutaneous nodules, which will allow a toxicity study of a greater range of patients and an increase in the accrual rate.
- Reduction of the upper age limit from 55 to 45 years to lower the risk of the presence of undiagnosed cardiac disease.
- Reduction of the number of intratumoral injections.
- Reduction of the top dose.
- A site change. The trial is now being conducted at Sharp HealthCare in San Diego, which has a catchment area of 1 million patients and thus an ability to provide an ample number of participants for a clinical trial such as this.
- Addition of positron emission tomography and dynamic magnetic resonance imaging (MRI) to obtain data on the functional response of the vasculature and tumor tissue.
- Changes to the informed consent document to make it compliant with the Health Insurance Portability and Accountability Act of 1996.

Dr. Deisseroth provided followup on the progress that has occurred in responding to the questions and issues raised by the RAC after its December 2000 in-depth public review. The first two questions raised the issue of a second animal model besides the mice that were being used and the ability to look at the exact construct proposed for the clinical trial. For several years, the investigators were unable to identify

a feasible animal model that would permit use of the exact construct, but then the investigators identified a colleague who had a transgenic mouse with human tissue factor being expressed in the animal in the absence of mouse tissue factor. In summer 2003 the investigators injected the animal with the immunoconjugate protein at dose levels that would generate levels in the bloodstream of the animals that were tenfold and a hundredfold in excess of what would be produced at the top dose of the proposed clinical trial. These animals were analyzed clinically and histochemically for signs of bleeding; the hemoglobin was examined, and the investigators found no evidence of bleeding, which was one of the major issues of concern to the RAC.

Another RAC question centered on the immunocompetent mouse, since most of the data were on the SCID mouse human tumor xenograft. Since 2000 the investigators have looked at syngeneic mouse tumor models, prostate cancer, melanoma, and breast cancer in small numbers of mice using controls; in each model, neither tumor regression nor toxicity was demonstrated.

Although the investigators had presented data comparing the binding of the immunoconjugate molecule to the vasculature of tumor tissue vs. normal vasculature in the liver and kidney, RAC members' comments noted that the investigators had not conducted a systemic survey of the entire animal. In the interim, the investigators have contracted with Molecular Diagnostics, Inc., to undertake three different analyses of biodistribution; the contract is signed, and the studies will begin in the next month or two. The first study involves intratumoral injection of the icon vector and then assaying the autopsies on the animals and assaying the organs to determine vector clearance. The investigators will inject separately the icon protein and the vector intravenously following clearance from the organs and the serum. Toxicity will be assessed under those conditions.

A. RAC Discussion

Dr. Bohn suggested that the investigators assay for neutralizing antibodies to the tetracycline activator because of reports in animal studies of the existence of those neutralizing antibodies; Dr. Deisseroth agreed.

Dr. L. Johnson suggested that the various cardiac and lung disease screening studies originally included in the protocol to determine participant eligibility be reincluded in the protocol, because there are individuals with no apparent history of these disorders but who have significant lung and cardiac disease that may not be picked up unless those kinds of screenings are conducted. Dr. Deisseroth thanked Dr. L. Johnson for his suggestion and agreed to consider adding such screening studies, even though the eligibility criteria include a long list of disease states that would make it nearly impossible for anyone with significant functional change in the lungs or heart to be admitted to the protocol.

VII. Discussion of Human Gene Transfer Protocol #0310-610: A Phase I/II Study of the Treatment of Recurrent or Progressive Malignant Glioma Using Autologous Bone Marrow-Derived Stromal Cells Nonvirally Transduced to Express Interleukin-12

Principal Investigator:	Tom Mikklesen, M.D., Henry Ford Cancer Center
Additional Presenters:	Alan K. Smith, Ph.D., Oncocidex, Inc., and Richard W. Slauter, Ph.D., Oncocidex, Inc.
Sponsor:	Oncocidex, Inc.
RAC Reviewers:	Drs. Bohn, Childress, Sidransky, and Wara
Ad hoc Reviewer:	Evan Y. Snyder, M.D., Ph.D., The Burnham Institute

A. Protocol Summary

Glioblastoma multiforme is a highly malignant form of primary brain tumor that is among the leading causes of cancer mortality in people younger than 54 years of age. Due to its expansive and infiltrative nature, it is nearly impossible to remove the tumor completely the first time it appears, which results in tumor recurrence in 80 percent of patients. Current therapies to treat the recurrence, such as local

radiation, chemotherapy, and surgical removal, have not proven effective. Using bone marrow-derived stromal cell-12 (BMSC-12) is a new treatment that is being studied to determine whether it can treat brain tumors that have recurred.

BMSC-12 is a combination of a person's own (autologous) bone marrow cells that have been expanded and then modified with the gene interleukin-12 (IL-12). In nonhuman animal studies, these BMSCs have been shown to have the ability to "find" tumors, and the IL-12 gene has been shown to attract immune cells to cancer cells, thus killing the cancer cells.

Studies of rats with glioma tumors used an injection of BMSC-12 with a dose of IL-12 that is 10 times greater than the dose proposed for this clinical trial. The animals in this study experienced no side effects from the BMSC-12 except slight anemia and a small drop in white blood cell count, side effects that are normal for IL-12. An ongoing study of whether BMSCs cause tumors in mice is only half finished, but after 3 weeks, no animals that have received BMSCs have any tumors.

Participants in this clinical trial must have a cancerous glioma that has grown back after removal at least once and must have received maximal radiation therapy. BMSCs will be harvested from each participant's hip, and the cells will be sent to Oncocidex, Inc., where they will be grown and combined with IL-12 to make BMSC-12. While the cells are growing, participants will undergo tumor biopsies and may have a catheter placed either in or near the tumor or tumor cavity in the brain. When the BMSC-12 is ready and the participant has recovered from biopsy surgery, the first dose of BMSC-12 will be given through the catheter or by stereotactic injection. Participants then will receive one dose a month for up to 9 months. It is hoped that the BMSC-12 will "find" the tumor, the IL-12 will attract immune cells to the tumor, and the immune cells then will kill the tumor. Each participant will have an MRI and will be closely monitored each time a new dose is given. In addition, every 2 months for 1 year after the previous dose of BMSC-12 is administered, participants will have an MRI to watch for any side effects of BMSC-12 and for tumor changes.

The study is designed to provide early evidence of the safety of this procedure and to provide an initial indication as to whether BMSC-12 is effective at finding and killing glioma tumor cells.

B. Reviews by RAC Members and *Ad Hoc* Reviewer

Ten RAC members voted for in-depth review and public discussion of this protocol, which involves a novel technology in the use of BMSCs genetically modified to express IL-12 followed by introduction of these gene-modified stromal cells into the brains of research participants with malignant glioma. Many conceptual, technical, and policy issues are raised by this protocol, and the informed consent documents do not fully capture the innovative nature of this study. RAC reviewers Drs. Bohn, Childress, Sidransky, and Wara and *ad hoc* reviewer Dr. Snyder submitted written reviews, to which the investigators responded in writing and during this meeting.

Noting that the whole world will be watching this protocol as it unfolds, Dr. Bohn acknowledged that the sponsor provided many data from mouse and rat studies that fundamentally inform the clinical application; however, several concerns remained: (1) The fate of the BMSCs with or without the IL-12 gene in the brain has not been studied rigorously, (2) the efficacy of this specific approach has not been demonstrated in a rodent model of glioblastoma, and (3) a rescue strategy might be necessary to address the possibility that this approach is successful in killing the tumor but results in unwanted behavioral or cognitive effects because of integrating new cells into brain parenchyma. Dr. Bohn suggested that IL-12 levels in plasma be assessed more regularly, at least at each treatment time.

Dr. Childress' review concentrated on the informed consent document, noting that overall the form appeared to include most of the relevant information but that it did not do so in an orderly or clear fashion. He noted that all the novel aspects of this protocol should be listed together, additional subheadings would be helpful in the section on risks and discomforts, language that overstates the therapeutic nature of the study should be changed, and clarification and consistency are needed for the formulations. To

ensure maximal clarity, Dr. Childress suggested that the form be copyedited to correct typographical errors, ensure subject-verb agreement, and smooth the flow of the text.

Although Dr. Sidransky did not attend Day One of this RAC meeting, his written review included the following concerns: (1) The oncogenic studies with nontransduced BMSCs in nude mice should be expanded to at least 26 weeks, (2) tumor assessment and regression should be described more thoroughly, (3) controlling transfection efficiency in human trials should be discussed, (4) efforts to track the cells using repeat biopsies should be considered, and (5) more information is needed about how the investigators will measure local and systemic IL-12 levels or other downstream cytokines.

Dr. Wara noted that the novel aspects of this protocol include that neither BMSCs nor the IL-12 gene have been injected into the human brain. Although the preclinical findings are extensive, well documented, and encouraging, she stated that there are no preclinical data in a rat tumor model that utilize the product to be tested and document the impact on human glioma. In addition, the dose proposed for the protocol—with repeated injections for 9 months—is not supported by the preclinical data. Dr. Wara stated that the proposed study is somewhat unusual for a Phase I study in that there is no dose escalation, the repeat-dose paradigm has not been proven safe, and there is no data and safety monitoring board (DSMB) evaluation after each group of three participants has been dosed. Dr. Wara also expressed concern about the presence of changes in the inflammatory track in the rat model as well as such changes in other human studies in which transgenes are injected into the central nervous system (CNS).

After noting that he supports the use of stem cell technology in the clinic, specifically for brain tumors, Dr. Snyder posed several concerns to the investigators. The preclinical data appear too preliminary to use this procedure in humans. He noted that (1) the scientific rationale for this protocol is insufficient, (2) neural stem cell (NSC) and glioma probably share a common biology, (3) it is dangerous to extrapolate from early stem cell data to adult cells and dangerous to extrapolate from the BMSCs of one laboratory to another, (4) new transgenic mouse models that develop invasive tumors that better mimic the human should be utilized in preclinical testing, and (5) significant limitations exist, such as not being able to start and stop the reaction or eliminate the cells if something goes awry. Several concerns could and should be tested in nonhuman animal models before moving to a clinical trial, such as whether these cells will become inappropriate nonneural cells that would hurt the host, what will happen with repeated doses of BMSCs especially without a method to remove them, and how effective IL-12 is in tumor growth. Dr. Snyder expressed his belief that a clinical failure now would tarnish the entire field of stem-cell-mediated approaches to pathology, including brain tumors. In addition, participants who enter this trial would be precluded from entering another trial that may have a better and longer history of efficacy and safety.

C. RAC Discussion

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

- Dr. Bohn suggested that the investigators consider replacing the Fischer 344 rat (an inbred strain) with an outbred rat strain for additional modeling.

- Dr. Wara suggested using dose escalation and repeated injections for the human trial.

- Dr. DeMets noted the need for both a marker of success in this small trial and a specification of the safety end points to match what would be expected for a Phase I trial involving 12 research participants.

- Dr. Bohn suggested that one of the study goals should be to understand the fate of the cells in the human brain by using a marker; plain histology would not provide adequate information. A nuclear marker using double staining might be used. If the result is coexpression with neuronal phenotypes, it is unlikely that those cells derive from macrophages.

- Dr. Simari questioned whether it is standard practice to leave an intratumoral catheter in place for the life of the individual.

- Dr. Borror expressed concern that the technical medical language and the ordinary words in the informed consent document are complex, using three- and four-syllable words when one- and two-syllable words would be adequate. The sentence structure is also overly complex. The language in this document should be simplified to make it easier to understand. The focus on safety needs to be reflected in the informed consent document, which currently focuses on efficacy and implies benefit. It should be stated that these first 12 research participants are unlikely to receive any benefit.

- Dr. Snyder summarized various concerns by stating that the investigators' obligation is to put the best cell into the brain with the best gene by the best route available, especially when cell, gene, and route options can be tested relatively easily preclinically. Empirical data can provide compelling rational and should be gathered.

- Dr. Snyder wondered whether IL-12 is the best of the interleukins to use or whether IL-6 should be compared.

- Dr. Snyder suggested that efficacy could be demonstrated beyond simply survival vs. no survival, such as measuring tumor burden, tumor migration, and residual cells.

- Dr. L. Johnson requested further clarification about whether NSCs should be used instead of BMSCs.

D. Investigator Response

Drs. Mikklesen, Slauter, and Smith responded with the following information:

- Although development of a better animal model is an avenue for further research, currently there is no animal model relevant to these brain tumors that would predict a response in the clinic.

- With regard to the safety of the catheter implant, the neurosurgeons for this Phase I trial have been consulted and have experience (in chemotherapy, for example) with implanting devices over the course of many months, with repeated administrations. Repeated catheter implant would be both safe and effective in delivering repetitive doses to the target.

- Any suggestions that the procedure in this trial may prevent recurrence of brain tumors will be removed from the informed consent document.

- Although the investigators in this study have a vested interest in NSCs, they nonetheless believe that other hurdles need to be addressed before NSCs could effectively be used in human clinical trials. The investigators did not believe it was required to show that BMSCs are better than NSCs, rather that there are sufficient data to support the use of BMSCs in human clinical trials as proposed.

- In brain tumor models, the animals are almost entirely well until the point at which they die suddenly, so a window of behavioral abnormality cannot be assessed. Behavioral studies in animals are not described in brain tumor models.

- The investigators are not fundamentally opposed to conducting a survival study but noted that the F98 tumor is uniformly lethal in 60 days. They are unsure of the appropriate regimen with which to treat an animal model to produce a result that will have meaning for the proposed 10-month human study.

- Regarding the use of dose escalation with repeated injections in the setting of recurrent glioblastoma, the investigators would consider themselves lucky to be able to continue to treat patients using that

schema, since a dose-escalation study completed in that manner would mean the individuals survived long enough to be administered the repeated doses.

- This proposed clinical trial might be more appropriately described as a pilot study to look at safety end points, with the goal of justifying a larger and more focused trial with conventional end points.

- Leaving a catheter in place peritumorally for the rest of an individual's life is a novel concept, although from a neurosurgical perspective it is considered safe and feasible. No surgeon with whom Dr. Mikklesen spoke raised any objection to the feasibility or safety of doing so.

- To simplify the interpretation of this study, the investigators believed it would be easier and safer to use autologous cells rather than to use allogeneic cells on top of the proposed therapies and IL-12. Allogeneic cells might put in jeopardy the ability to deliver multiple doses and use an allogeneic cell product; if a memory response occurs, there may be a problem with the second or third administration, which would pose a potential safety risk.

- With regard to the expression window of IL-12, cells that were transplanted into the opposite side hemisphere in the rat model were found in tumors within 24 hours. The cells arrive in the locale of the tumor well within the window of opportunity for maximal expression of IL-12.

- Some of the tumor cells might survive this procedure and potentially give rise to even more invasive tumors. These patients' lifetimes are measured in weeks rather than months, but the potential of selection for more virulent tumor cells exists in most of the clinical antineoplastic therapies currently employed.

E. Public Comment

No comments were received from the public.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC comments and recommendations:

- Some RAC members continue to be concerned about the choice of delivery cell (BMSC vs. NSC). Although the choice of cell may not be ideal, the purpose is not to wait until ideal conditions exist but to use what is available.

- Additional longer term studies are recommended because of the pervading sense of RAC members that long-term safety studies have not been performed to the most optimal time point.

- Survival studies should be performed in a suitable nonhuman animal model, since this is important to the interpretation of this protocol and to the feasibility of learning what is proposed.

- The investigators need to obtain preclinical data in a rat tumor-bearing model and study the fate of those cells.

- Contralateral distribution of the cells from the striatal bed, the speed and source for that distribution, and the potential for confounding mechanisms may deserve additional study.

- Despite the limited life expectancy of these research participants, some shutoff or suicide mechanism is needed. To understand what these cells are doing and where they go, the investigators are advised to incorporate a transgene shutoff mechanism.

- Further discussion of experience with and rationale for long-term catheter implantation into a tumor bed is needed, with comments specific to glioblastoma.

- Behavioral studies should be conducted in tumor-bearing animals, with and without IL-12 and with and without genetically modified BMSCs.

- The consent form should be changed to remove confusing language, deemphasize the therapeutic goals, and emphasize the safety goals of the study.

- The exclusion criteria should be amended to include individuals whose tumors are close to ventricles.

- The use of allogeneic vs. autologous cells deserves additional comment. If the goal is to induce an immune response, allogeneic cells may be more effective; the investigators may want to consider a comparative study of the two.

- The investigators should more tightly define the goals of the study so they can more critically justify the proposed number of participants, which is 12. The ability to achieve the study's goals is a function of how concisely those goals are expressed.

- The investigators are invited to return to the RAC after discussions with the FDA and after other changes and recommendations have been taken into account. RAC members requested that they be kept apprised of the development of this protocol and how the RAC's recommendations influence study design.

G. Committee Motion 2

It was moved by Dr. L. Johnson and seconded by Dr. Gelehrter that these recommendations expressed the comments and concerns of the RAC. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

H. Further RAC Discussion

Ms. Kwan requested that the OBA word the letter to the investigators to make it explicit that the sending of the letter along with the RAC's recommendations does not constitute either approval or disapproval of the proposed protocol. She was concerned that public pronouncements by sponsors have wrongly characterized letters sent after public RAC review as "approval." Dr. Rose noted that the OBA would work on the wording but that statements by other parties could not be controlled.

VIII. Educational Seminar Series on Retroviruses: "Different Global Genomic Preferences for MLV and HIV-1 Proviral Integration"/Shawn M. Burgess, Ph.D., NHGRI

Dr. Burgess described his studies of zebra fish genetics in which retroviral or lentiviral vectors are used to induce mutations in the zebra fish genome. Because of the availability and quality of the human genome sequence, integrations were studied first in the human HeLa cell line as a proof of principle study. The HeLa cells were transfected with either an MLV-based vector or HIV-1 based vector. After 48 hours incubation, the genomic DNA was isolated, linker mediated PCR was performed to amplify sequence adjacent to the proviral integrations for high-throughput cloning, and the sequence mapped to RefSeq genes in the human genome. The MLV vector was found to have integrated into a gene in 32% of integrations. For HIV-1, 58% of the integrations occurred in a gene. The results were statistically different between the two types of viral vectors and from the result of 22% random integrations into genes. Analysis was also performed to determine whether there were differences in where the different viruses integrated within a gene. 17% of MLV integrations were within 1 kb of CpG islands which are associated with transcriptional start sites in vertebrate genes. HIV-1 and random integrations were observed in that region in only 2% of integrations. For HIV-1, the percentage of integrations was higher than random across the entire gene sequence. Microarray data was used to examine the expression level of the genes in which MLV integrated. The data suggested that MLV preferred to integrate into more actively transcribed genes.

In the gene transfer field, the risk of insertional mutagenesis by retroviral vectors was considered to be low because it was based on the assumption of random integration. According to the results of this study, 20% of MLV integrations occurred within 5 kb up- or downstream of transcriptional start sites. In the two leukemia cases in the French X-SCID trial, the MLV vector had integrated into this region of the LMO-2 gene. Given the dose of transfected cells used in the trial, approximately 220 cells would be predicted to have integrations into LMO-2.

Dr. Burgess concluded that MLV prefers to integrate near transcriptional start sites, while HIV-1 prefers the entire transcription unit. The different integration preferences of different viruses may reflect the involvement of different cellular factors; therefore each vector may have different associated risk factors. MLV vectors may be more likely to misactivate genes while HIV-1 vectors may more likely inactivate genes. Vectors based on different viruses should be tested in different target cells.

A. RAC Discussion

Dr. Friedmann asked why the first research participant with leukemia in the French X-SCID study had a single integration into LMO-2 and the second research participant had three rather than the possible 200 cells with LMO-2 integrations. Dr. Burgess responded that other factors involved may include the repopulation efficiency of the transfected cells, the selective advantage associated with LMO-2, and the possibility that multiple hits are necessary to cause oncogenesis.

Dr. DeLuca asked whether an HIV-1 based vector would be preferable over an MLV-based vector for uses such as the X-SCID gene transfer. Dr. Burgess replied that the risk of oncogenesis associated with HIV-1 vectors may more likely be due to integration into a tumor suppressor gene and require a second mutation of the other allele. Therefore, the relative risk of oncogenesis may be lower than for MLV vectors which may be more likely to integrate and activate transcription of an oncogene.

Dr. Friedmann asked if the different viral integration preferences were also seen in other cell types. Dr. Burgess responded that similar results were observed in mouse cells. The MLV results were similar in zebra fish.

IX. Day One Adjournment/Dr. Friedmann

Dr. Friedmann adjourned the first day of the December 2003 RAC meeting at 4:45 p.m. on December 3, 2003.

X. Day Two Opening/Dr. Friedmann

Dr. Friedmann opened the second day of the December 2003 RAC meeting at 8:30 a.m. on December 4, 2003.

XI. Discussion of Human Gene Transfer Protocol #0307-589: A Phase I Study in Glaucoma Subjects Receiving SCH 412499 (rAd-p21) Administered as a Single Injection Into the Subconjunctival Space Prior to Primary Trabeculectomy

Principal Investigators:	Paul L. Kaufman, M.D., University of Wisconsin Medical School, Madison, and Robert N. Weinreb, M.D., University of California, San Diego
Additional Presenters:	Robert W. Veneziale, Ph.D., Schering-Plough Research Institute, and Daniel C. Maneval, Ph.D., Canji, Inc.
Sponsor:	Schering-Plough Research Institute
RAC Reviewers:	Dr. DeLuca, Ms. Kwan, and Dr. Simari

Ad hoc Reviewer: Donald L. Budenz, M.D., Bascom Palmer Eye Institute

Dr. Friedmann recused himself from discussion of and voting on this protocol because of a conflict of interest. Dr. Wara chaired the RAC for discussion of this protocol.

A. Protocol Summary

Glaucoma is the leading cause of irreversible blindness in the United States and the rest of the world. The disease is characterized by elevation of intraocular pressure (IOP), resulting in degeneration of the optic nerve and loss of vision. The majority of therapies to treat glaucoma are directed at lowering IOP. Glaucoma filtration surgery (trabeculectomy) reduces IOP through a procedure that creates a small drainage hole in the eye. Glaucoma surgery failure results from a normal wound-healing response that blocks the surgically created hole. This healing causes IOP to rise again, indicating that the surgery has failed. Part of this wound-healing response is due to the growth of cells at the surgical site. The failure rate is as high as 50 percent after 2 years and higher in certain patients. Drugs that block cell growth have improved the long-term success rate of this surgery; however, these drugs have been associated with serious side effects, some of which can be blinding. As such, there is a need to develop an improved method of preventing surgical failure without these side effects.

This Phase I study will determine the safety of a gene transfer drug that is designed to block the cell growth noted above. The gene p21WAF1/CIP1, whose normal function in a cell is to inhibit growth, will be delivered to the eye. Carried by an adenovirus, the gene will be delivered by injection under the conjunctiva 1 day prior to surgery.

Laboratory experiments have shown that this gene-virus combination (called SCH 412499) inhibits the growth of cells in the eye. Surgical studies in rabbits have shown that SCH 412499 prolongs surgical success when delivered 1 day before surgery. Treatment with SCH 412499 in the eyes of monkeys with high IOP resulted in the lowering of IOP following trabeculectomy. The side effects seen with other drugs have not been seen with SCH 412499 in either rabbits or monkeys. Decreasing IOP is the goal of future clinical trials with SCH 412499. Nonclinical safety testing in monkeys has been completed, and the results support the initiation of human trials. The proposed clinical study intends to look at the safety of SCH 412499 in humans.

B. Reviews by RAC Members and *Ad Hoc* Reviewer

Eleven RAC members voted for in-depth review and public discussion of this protocol. This protocol involves a novel gene transfer approach as an adjuvant to surgery for glaucoma, the use of a new construct, a new transgene for gene transfer, and a new glaucoma patient population with a potentially long lifespan after gene transfer. RAC reviewers Dr. DeLuca, Ms. Kwan, and Dr. Simari and *ad hoc* reviewer Dr. Budenz submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. DeLuca applauded the investigators for a well-written and nearly comprehensive protocol that included extensive preclinical *in vitro* and *in vivo* efficacy and safety studies. Acknowledging that the summarized outcomes of these experiments support the proposed clinical trial, Dr. DeLuca requested that the investigators provide the primary data and details of their methodologies. Additional specific questions addressed the long-term outcome of the infectious effect of the rAd-p21 on cell growth and cell cycle arrest in culture; the outcomes as a function of dose in rabbit and monkey models for the extent and duration of p21 expression, the extent and duration of inflammation, antibody response to adenovirus, and IOP; whether the biodistribution studies were performed in the brain and trigeminal ganglia and other specifics about the biodistribution studies; and whether p21 expression inhibits the production of the vector on complementing cell lines.

Ms. Kwan requested a clearer description and explanation of the specific occurrences that result in trabeculectomy failure and an explicit accounting of when these changes occur. A clear hypothesis is needed of how the gene transfer mechanism offers a greater chance of intermediate or long-term

success than does either 5-fluorouracil (5-FU) or mitomycin C—two cytotoxic chemotherapeutic agents that, when used off label, appear to reduce scarring. The time interval and reason for selecting that interval between dose escalations need clear definition and explanation, and the number of participants should be clarified as well as the reason for selecting that number. A request for autopsy should be included in the informed consent document.

Dr. Simari requested more details regarding the biodistribution studies, specifically the distribution of vector in neurons. Questions about the preclinical studies included how the model, delivery, and dose represent the clinical scenario; whether there is reason to believe that transduction of human cells *in situ* will reflect the animal studies; how the surgical procedure affects the distribution and expression of the viral vector; whether the cytostatic intent of the proposed approach has been proven in animals; and whether a preclinical model exists to estimate what might occur if a participant refuses surgery following vector delivery. Questions about the trial design included whether there are any inherent ophthalmologic processes that require proliferation and whether there are risks of inhibition using this approach, the length of time over which the vector will be injected, whether certain features place participants at higher risk of abnormal healing, the risk of incomplete healing with this approach, and whether it is possible to obtain distribution and expression data by examining excised tissue. Dr. Simari clarified that glaucoma is a disease with many treatment options; this protocol seeks to prevent the side effects of treatment, not to treat patients who have no other treatment options.

Dr. Budenz acknowledged that the protocol was comprehensive and suggested that the investigators justify the use of adenoviral-mediated transfection rather than an AAV, which has been shown to be less inflammatory. More detail is needed on the effect of p21 transfection in other cells locally, particularly limbal stem cells and CNS cells. The number of participants to be enrolled should be clarified. Further justification is needed for the use of this experimental method in primary, rather than refractory, glaucoma surgery. The investigators should consider taking a sample of Tenon's layer for analysis of transfection at the time of surgery. The main recommendation from Dr. Budenz that remained to be addressed was a careful evaluation of the limbal cells in participants over time to pick up any adverse effect on the corneal surface at the microscopic level.

C. RAC Discussion

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

- Dr. Gelehrter wondered how much of a role is played by extracellular matrix deposition. Efficacy data with antimitotics and with p21 indicate that cell proliferation is an important part of the pathogenesis of the wound-healing and fibrosis problems.

- Ms. Kwan expressed concern about the off-label use of mitomycin C and 5-FU and potential, future complications. She queried whether a paper should be presented to warn people of this use.

Several RAC members noted that the informed consent document was particularly complete and well written.

D. Investigator Response

Drs. Kaufman, Maneval, Veneziale, and Weinreb responded with the following information:

- In the monkey studies, the investigators saw no ocular surface problems at all; the monkeys' eyes were clean. Also in the monkey studies, initially no corneal changes were noted with subconjunctival injection of 5-FU. However, widespread clinical use of 5-FU has resulted in some corneal changes. Therefore, during this clinical trial, corneas will be monitored carefully as will limbal cell populations.

- When conducting a trabeculectomy, a piece of conjunctiva and a small amount of subconjunctival tissue are taken, and a piece of peripheral cornea usually is also obtained; all of these tissues could be examined.

- The investigators have been able to culture primary ocular fibroblasts only for about a week. However, in *in vivo* primate experiments, the investigators were able to sustain the experimental animals for 8 ½ months. The signals for proliferation should occur within the first few weeks; consequently, the transgene expression should be high during that time *in vivo*. The long-term cell culture *in vitro* experiments are not easily conducted, so the investigators have not conducted them with ocular fibroblasts.

- Most glaucoma patients are controlled with eye drops, but those who have glaucoma long enough are likely to find that eye drops will not be adequate and that laser trabeculoplasty will be indicated. Laser trabeculoplasty is typically a temporary solution, and trabeculectomy is indicated; it is estimated that possibly 100,000 to 200,000 trabeculectomies are performed in the United States each year. One of the antiproliferative agents—either 5-FU or mitomycin C—is commonly used with the trabeculectomy. In patients who undergo trabeculectomy with those agents, as more time elapses after surgery, it becomes more likely it is that their conjunctiva will break down and that one of the possible side effects, including infection in the eye, will occur.

- Neither 5-FU nor mitomycin C has been approved by the FDA for use with glaucoma surgery, yet clinicians are using these antiproliferative agents for that purpose. The side effect profile of each is known, but the epidemiology is unknown. Mitomycin C is typically applied intraoperatively at the time of surgery and then is washed away; 5-FU is more commonly applied subconjunctivally at the time of surgery and/or following surgery, using repeated injections. Mitomycin C and 5-FU are currently used commonly, and there is significant concern about the complications that will arise in years hence. Although the basic problems remain, attempts to minimize the potential complications of mitomycin C have included changes in the technique by which it is applied, the dosage used, and the amount of time it is allowed to remain on the eye.

- The investigators decided to select for inclusion patients who were not at highest risk because they believed that the highest risk patients deserved the best chance of success, which is the standard therapy.

- Little is known about the role of extracellular matrix deposition. An alternative therapy currently in clinical investigation uses an antibody for TGF-β to alter the proliferative and extracellular matrix response.

- The investigators looked at and compared other cell cycle regulators in culture, including p53 and p16. The p21 regulator was chosen for the human trials because of its activity in the animal models, but more research is needed.

E. Public Comment

No comments were received from the public.

F. RAC Recommendations

Dr. Wara noted that only one concern remained: the long-term outcome of p21. Thus, the RAC recommended that additional preclinical data be generated to address the ratio of dying to proliferating cells, as well as other aspects of *in vivo* cell culture, and that research participants in the clinical trial be provided with careful long-term followup of corneal cells. In addition, several reviewers mentioned the extraordinary opportunity to capture tissue obtained at the time of surgical procedure, which could be used to look for Ad-p21 and for events such as apoptosis in conjunctival and subconjunctival tissue at the time of surgery. It was noted that the additional preclinical data could be collected in parallel with the Phase I trial, and the importance of long-term followup of research participants was stressed.

G. Committee Motion 3

It was moved by Dr. L. Johnson and seconded by Ms. Kwan that the above recommendations expressed the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 0 abstentions, and 1 recusal.

XII. *NIH Guidance on Informed Consent for Gene Transfer Research*—A Web-Based Resource

Presenters: Nancy M.P. King, J.D., University of North Carolina, Chapel Hill, and Sue L. Levi-Pearl, Tourette's Syndrome Association, Inc.

Ms. King discussed the completed *NIH Guidance on Informed Consent for Gene Transfer Research*, a document that was developed during the past 2 years by members of the RAC with other expert input. The primary intended users of this guidance are PIs; additional potential users are IRBs, IBCs, research sponsors, potential research participants, and the public. The guidance is an educational tool and an information resource about how to use current policy to best advantage; it is not an amendment to Appendix M of the *NIH Guidelines*, and it does not represent new policy. It was developed to assist investigators and other users in understanding gene transfer research, writing better informed consent documents, and creating a more effective consent process.

Although this specific document has been in development for nearly 2 years, the concerns of RAC members about informed consent go back at least 10 years to the early review of clinical trials in gene transfer, when the RAC first noted that science and ethics could not be separated completely. To this day, the RAC still sees inadequate informed consent documents attached to protocol proposals and is still hearing that IRBs and investigators do not know where to obtain guidance about how to write an acceptable informed consent document.

Many draft iterations were presented to the RAC and the OBA during the past year, and a near-final version was presented at the June 2003 RAC meeting. After incorporating RAC, OBA, and public suggestions, this document was posted on the OBA Web site on December 3, 2003, at <www4.od.nih.gov/oba/rac/ic>.

Ms. King acknowledged the Informed Consent Working Group members, agency representatives, and OBA staff members who contributed to this document, especially Dr. Brody, who cochaired this effort. Other individuals involved in creating and massaging this document included current RAC members Drs. Childress, Lo, and Wara; Ms. Sue Levi-Pearl, a former RAC member; Dr. Christina Borror, NIH Office for Human Research Protections (OHRP); Dr. Cynthia Rask, FDA; OBA summer interns Ms. Suzanne Goodwin, Ms. Katherine Heineman, and Ms. Courtney Storm; and OBA staff members Dr. Amy Patterson, Dr. Rose, and Mr. Shipp.

Ms. King demonstrated the document on the OBA Web site, showing the hot links, the ability to jump to various parts of the document, and sample language provided in drop-down boxes. As new guidance emerges, all links will be updated.

Mr. Shipp, Ms. Goodwin, and Ms. King will be conducting a workshop on this guidance at the PRIM&R annual meeting, and at as many other venues as possible, to make potential users aware of its availability.

Much of the material in this guidance is relevant and will be useful beyond gene transfer research and can inform researchers in other disciplines and other trials and participant populations.

A. RAC Discussion

The following ideas for publicizing this resource were discussed:

General multicontact ideas:

- Penetrate corporate offices.

- Inform patient groups so research subjects know how to ask the appropriate questions.

- Provide information about this resource to all the advocate groups and societies associated with protocols the RAC has reviewed to date. These same groups should be asked for their continued input for improving the guidance.

- Encourage local review committees to incorporate an active review of this resource into their training of committee members and their contact with investigators.

- Inform science writers of the availability of this resource.

Professional group in-person contact ideas:

- Instruct or encourage IBCs and IRBs to make investigators aware of this guidance at an early stage.

- Use this guidance as a teaching resource at research institutions, for example, as part of required research training for investigators and research staff members.

- Sponsor a half- or full-day workshop focusing on how to increase the use of this document and what changes consumers view as potentially useful. Invite representatives of the broadest spectrum of users—for example, academic institutions, OHRP, corporations—to obtain input on how to get this guidance known and used. This workshop could be offered as a half-day session in conjunction with a RAC meeting.

- Showcase this guidance at the American Society of Gene Therapy (ASGT) annual meeting.

- Highlight this resource at relevant national and regional professional meetings and conferences attended by investigators. It is unlikely that they would travel to a special meeting on this topic.

Online contact ideas:

- Notify and actively request that other relevant agencies link their information to this guidance document. Network among other Federal agencies and offices to let them know that this document is a resource for all human studies, not just gene transfer.

- Post information and a link on bioethics Web sites. Every bioethics Web site has a resource list.

Print contact ideas:

- Publish information about this resource in *OBA News*, to which many IBCs subscribe.

- Issue a press release.

- Write op-ed pieces.

- Write an editorial for *Science*.

- Create and distribute a flyer that advertises this resource. The flyer should advertise the site and give a succinct summary of what is available.

- Ask the editor of the ASGT journal *Molecular Therapy* to write an editorial featuring this informed consent document guidance.

Ms. King stated that the working group would remain constituted to discuss a list of the different publicity avenues and to formulate a recommendation to the RAC regarding how to maximize this resource.

XIII. Discussion of Human Gene Transfer Protocol #0307-592: A Phase I Study to Determine the Safety and Immunogenicity of Vaccination With *Listeria Monocytogenes* Expressing Human Papillomavirus Type 16 E7 for the Treatment of Progressive, Recurrent, and Advanced Squamous Cell Cancer of the Cervix

Principal Investigator:	John Marshall, M.D., Georgetown University Medical Center
Additional Presenters:	James P. Patton, M.D., Advaxis, Inc.; Yvonne Paterson, Ph.D., University of Pennsylvania; and Thorston Verch, Ph.D., University of Pennsylvania
Sponsor:	Advaxis, Inc.
RAC Reviewers:	Drs. Barkley, L. Johnson, and Lo

Dr. Powers recused himself from discussion of and voting on this protocol because of a conflict of interest.

A. Protocol Summary

Approximately 60,000 new cases of cervical cancer are diagnosed each year, and the overall 5-year survival rate for cervical cancer is 71 percent. Early detection by routine screening of preneoplastic lesions has made a serious impact on cervical cancer mortality in the Western hemisphere. However, cervical cancer is still the second leading cause of cancer death among women worldwide and a significant cause of cancer death among poor and uninsured women in the United States. About 50% of cervical cancer is the result of transformation by Human Papilloma Virus (HPV) strain 16.

Because squamous cell carcinoma of the cervix as a result of transformation by HPV is associated with the HPV transforming proteins E6 and E7, antigens for E6 and E7 have been an intense focus of cancer immunotherapies using a variety of vaccine vectors. Because of the intracellular localization of these antigens, these therapies are mostly directed at cellular immune responses. *Listeria monocytogenes* (Lm) has been shown to be an unusually potent stimulator of cellular immune responses to secreted antigens, including recombinant antigens that the bacterium has been engineered to express and secrete. Lm-LLO-E7 is a novel recombinant therapeutic cancer vaccine that is comprised of live, attenuated *L. monocytogenes* bacteria, which are genetically modified to express HPV type 16 E7 tumor antigen, linked to listeriolysin O (LLO) protein. When the engineered *Listeria* (Lm-LLO-E7) are introduced to the body, they are engulfed by antigen presenting cells in the immune system. The bacteria enter the cytoplasm of the cells and produce the LLOE7 protein. This protein is then degraded and presented on the surface of the cells thereby producing an immune response. Specifically, antigen presentation signals immune effector cells, especially cytotoxic T lymphocytes, to recognize and kill cells presenting this antigen. Additionally, some of the LLO E7 antigen produced by the *Listeria* is processed by the immune system to stimulate a lymphoproliferative response. In mouse tumor models Lm-LLO-E7 has been shown to increase survival and induce regression of tumors immortalized by HPV.

Because this agent has not been used in human trials to date, this preliminary Phase I study will be conducted in individuals with advanced disease for whom no standard effective curative or palliative therapy is available. A major consideration is the safety of using a live bacterium in potentially immunocompromised advanced cancer patients who may have received heavy pretreatment with radiation and chemotherapy. *Lm* is responsible for clinical infections, and clinical listeriosis has been shown to be treatable with a wide range of antibiotics in both immune-competent and immune-compromised individuals. In addition, the pathogenicity of Lm-LLO-E7 is significantly reduced; in mouse studies, the engineered bacteria are roughly 3,000 times less deadly than the wild-type *Lm*. As an added safety measure for the proposed clinical study, the investigators will incorporate antibiotic intervention to ensure clearance of the vaccine.
Patients will receive Lm LLO-E7 administered intravenously every 21 days for a total of three treatments. The primary objective of this study is to establish the safety and tolerability of vaccination with Lm-LLO-

E7. The secondary objective of this study is to determine the type of immunity induced against E7 delivered by the vector and its relationship to the number of organisms delivered in the vaccine.

B. Reviews by RAC Members

Fifteen RAC members voted for in-depth review and public discussion of this protocol, citing the limited experience with studies involving live bacteria as gene delivery vectors. RAC reviewers Drs. Barkley, L. Johnson, and Lo submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Barkley was generally concerned about the risk to research participants, noting that *Lm* is a moderate-risk human pathogen that can cause severe disease in susceptible individuals. Although the investigators have recognized this concern, he stated his belief that data presented in the protocol were not sufficient to state that the *Lm* vector would be significantly attenuated and therefore an acceptable risk to participants at the proposed dosing levels. *Lm* infection can cause meningitis, septicemia, and shock, and although infection is uncommon, elderly participants with malignancies and participants receiving immunosuppressive agents are highly susceptible to disease. He asked about the preclinical study in which one of four rhesus monkeys died of toxic shock. He noted that the infectious dose may differ when the vector is administered by i.v. rather than by ingestion. Dr. Barkley also expressed concern that some statements in the informed consent document might cause research participants to believe the risks to their health would be lower than they might actually be.

Dr. L. Johnson noted that the i.v. route of administration of a human pathogen, even as an attenuated vector, to individuals with advanced carcinoma raises several safety and protocol concerns. He noted that the trial should be characterized as a Phase I study. Regarding the route of administration, he also had safety concerns about i.v. administration, however he was satisfied with the data indicating that this was the most efficacious route. He asked whether the i.v. toxicology and biodistribution data were available. He recommended public health measures to prohibit pregnant or immunocompromised individuals from coming into contact with study participants. The informed consent document should reference the risks of sepsis, meningitis, and death. In addition, it should include information about the experimental nonhuman primate that died from toxic shock after receiving the highest dose.

Dr. Lo noted that the safety studies of the vaccine in nonhuman animals needs to be presented in more detail. The current informed consent document does not adequately convey the risks of the vaccine in immunocompromised individuals, and in light of the potential serious risks, the animal safety data should be summarized in the document. Dr. Lo requested further discussion about permitting dose escalation even if one of five participants at the current dose develops a dose-limiting toxicity such as meningitis, persistent bacteremia, or clinical sepsis.

C. RAC Discussion

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

- Dr. Friedmann asked about the fate of intracellular *Lm*.

- Dr. L. Johnson requested that the informed consent document make clear that participants might develop sepsis or meningitis. Even if the meningitis is treated, they could be left with significant neurologic sequelae from which they could potentially die.

- Dr. Sidransky stated that toxic shock cannot be controlled in the clinic. Patients with toxic shock live or die based primarily on what happens to them in the first few hours. Although the likelihood of a clinical trial participant developing toxic shock is very low, there is a risk of death that should be discussed in the informed consent document.

- Dr. DeMets suggested that the investigators clarify the primary and secondary goals of the study.

- Dr. Sidransky and Dr. P. Johnson pointed to the need to add information to the consent form stating that one of the experimental monkeys had died.

- Dr. McDonald asked how participants who are allergic to penicillin will be handled and suggested either that such individuals be excluded from this trial or that an alternative strategy to ampicillin administration be developed.

D. Investigator Response

Drs. Marshall, Paterson, Patton, and Verch responded with the following information:

- The rhesus study involved administering vector doses of between 10^9 and 10^{12} to a set of monkeys, using a vector that is more virulent than the one proposed for the human trial. Those doses were tolerated well, except for the 10^{12} dose that was given to two monkeys; one of those monkeys died of a toxic shock-like disease. The investigators are planning to conduct another study in monkeys using the vector to be used in the clinical trial. The 10^9 starting dose was chosen because monkeys tolerated the doses of 10^9, 10^{10}, and 10^{11}

- The total number of monkeys examined was eight in the first study which used the listeria vector with a different plasmid, and the investigators are planning to use six monkeys in the next study using the vector proposed for the human trial.

- The IV toxicology study has not been conducted yet. The SCID mouse does not have any adaptive immunity but is still able to clear the listeria using innate immunity. A nonhuman primate study is planned, and in-depth, longer term biodistribution data in mice will be available to be presented as part of the final investigational new drug submission to the FDA.

- The mouse is the recognized model for listeriosis. The construct to be used in this clinical trial is cleared rapidly in both normal and SCID mice; however, wild-type listeria sets up a chronic infection in SCID mice that is not cleared, and even sublethal doses kill 20 percent of the mice. The remainder of the mice had a chronic infection with microabscesses in the spleen and liver. This does not occur with the proposed construct, which is cleared by innate immunity. It is still important to look at the infection rate in the macaque, even though unlike mice, nonhuman primates are not available with specific defects.

- Bacteremia is not often observed with listeriosis. Within a few hours, the bacteria become intracellular, traffic to the liver and spleen, and then are cleared.

- With meningitis and many other serious infections, the key factor in successful treatment is how quickly antibiotic therapy is initiated and the efficacy of that therapy for the bacteria being treated. In the proposed trial, the investigators will know exactly when listeriosis symptoms are initiated and be able to start accurate and prompt antibiotic therapy if necessary.

- In general, patients with listeriosis are not treated as if they have an infection control problem and are not isolated. However, the investigators agreed with Dr. L. Johnson's recommendations.

- The levels of listeria being given to these patients should be cleared rapidly. Intervention with antibiotics is included in the protocol to add a measure of safety. On day 5, participants will receive an IV dose of ampicillin, and then they will be sent home on 10 days of oral antibiotics. If someone develops a serious case of bacteremia or meningitis, the recommended dose of antibiotic will be administered. The investigators would consider either excluding participants allergic to penicillin or developing a plan for the use of an alternative antibiotic.

E. Public Comment

No comments were received from the public.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations:

- The same GMP produced vector to be used in the clinical trial should be used for the toxicology studies and the studies should use a sufficient number of non-human primates to achieve statistical significance.
- To enhance the safety of research participants, the Data Safety Monitoring Board (DSMB) should be convened after the first occurrence of a serious adverse event such as sepsis, septic shock, or meningitis.
- Section 6.4 states that no interim analysis is planned for the study, while section 8.8 indicates that an interim analysis by the DSMB will be conducted. These discrepancies need to be resolved.
- Given the virulence of the vector used in the protocol (Listeria), additional steps should be taken to reduce the chances of its inadvertent transmission. Immunocompromised or pregnant individuals, including health care workers, should not be exposed to research participants until the participants have completed antibiotic treatment.
- The protocol and informed consent document should explain how research participants who are allergic to penicillin will be protected against Listeria infection. The investigators should discuss with their Institutional Review Board such options as the addition of an exclusion criterion or the establishment of a plan for using alternative antibiotics. Because the use of an alternative antibiotic could possibly complicate the interpretation of the clinical results, the investigators should consider performing preclinical studies to compare the use of the alternative antibiotic to penicillin in the animal model.
- Information should be added to the informed consent document clearly explaining that: 1) septic shock, other serious infectious complications, or death are risks of participating in the study; 2) adverse events such as these are possible despite antibiotic treatment; and 3) estimates of the likelihood of such events in research participants may not be predicted accurately by the non-human primate studies. This information also should be conveyed to potential subjects during the consent process. The investigators should confer with their IRB about this recommendation.

G. Committee Motion 4

It was moved by Dr. Gelehrter and seconded by Dr. P. Johnson that these recommendations expressed the comments and concerns of the RAC. The vote was 13 in favor, 0 opposed, 0 abstentions, and 1 recusal.

XIV. Closing Remarks and Adjournment/Dr. Friedmann

Dr. Friedmann thanked the participants and adjourned the meeting at 2:50 p.m. on December 4, 2003.

[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.]

_____

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:

_____

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Attachment I
Recombinant DNA Advisory Committee

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Jan Chappell, AnGes, Inc.
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Martin Giedlin, Cerus
Joanne S. Hawana, F-D-C Reports, Inc.
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Patricia D. Williams, TherImmune Research Corporation
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Attachment III
Abbreviations and Acronyms

5-FU	5-fluorouracil
AAV	adeno-associated virus
AE	adverse event
AIDS	acquired immune deficiency syndrome
ARENA	Applied Research Ethics National Association
ASGT	American Society of Gene Therapy
BMSC-12	bone marrow-derived stromal cell-12
CNS	central nervous system
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
FDA	U.S. Food and Drug Administration
HIV-1	human immunodeficiency virus type 1
HPV	human papillomavirus
IBC	institutional biosafety committee
IL-2	interleukin-2
IL-12	interleukin-12
IOP	intraocular pressure
IRB	institutional review board
IV	intravenous
Lm	*Listeria monocytogenes*
MLV	murine leukemia virus
MRI	magnetic resonance imaging
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NSC	neural stem cell
OBA	NIH Office of Biotechnology Activities
OD	NIH Office of the Director
OHRP	NIH Office for Human Research Protections
PCR	polymerase chain reaction
PEDF	pigment epithelium-derived factor
PI	principal investigator
PRIM&R	Public Responsibility in Medicine and Research
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
VEGF	vascular endothelial growth factor
X-SCID	X-linked severe combined immunodeficiency disease