RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 14-15, 2001

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 <www.nih.gov/od/oba/docs.htm>.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]
June 14-15, 2001

The Recombinant DNA Advisory Committee (RAC) was convened for the 82nd meeting at 8:30 a.m. on June 14, 2001 at the National Institutes of Health (NIH), Building 45, Natcher Conference Center, Conference Room D, 9000 Rockville Pike, Bethesda, MD 20892. Dr. Claudia A. Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 6:25 p.m. on June 14 and from 8:30 a.m. until 2:35 p.m. on June 15. The following individuals were present for all or part of the meeting:

Committee Members

C. Estuardo Aguilar-Cordova, Harvard Gene Therapy Initiative
Dale G. Ando, Cell Genesys
Xandra O. Breakefield, Massachusetts General Hospital
Louise T. Chow, University of Alabama-Birmingham
Jon W. Gordon, Mount Sinai School of Medicine
Jay J. Greenblatt, National Cancer Institute (NCI), NIH
Eric T. Juengst, Case Western Reserve University
Nancy M.P. King, University of North Carolina-Chapel Hill
Sue L. Levi-Pearl, Tourette Syndrome Association
Ruth Macklin, Albert Einstein College of Medicine
M. Louise Markert, Duke University Medical Center
Claudia A. Mickelson, Massachusetts Institute of Technology

A list of all RAC members and their affiliations and contact information appear in Attachment I.

Executive Secretary

Amy P. Patterson, NIH

Ad Hoc Reviewers/Speakers
Roy A.E. Bakay, Rush University and Rush-Presbyterian/St. Luke's Medical Center
Wendy Baldwin, NIH
Neal DeLuca, University of Pittsburgh
Howard J. Federoff, University of Rochester School of Medicine and Dentistry
David J. Fink, University of Pittsburgh
James B. Kaper, University of Maryland School of Medicine
Karen Midthun, Food and Drug Administration (FDA)
Gary Nabel, NIH
Michael Pensiero, National Institute of Allergy and Infectious Diseases (NIAID)
Robert D. Simari, Mayo Clinic
Carol O. Tacket, University of Maryland School of Medicine

Nonvoting/Agency Representatives
Kristina C. Borror, Office for Human Research Protections
Philip Noguchi, FDA
Stephanie L. Simek, FDA

[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.

NIH Staff Members
Lisa August, Office of the Director (OD)
Scott Cairns, NIAID
Sarah Carr, OD
Lydia Falk, NIAID
Kelly Fennington, OD
Aaron Goldenberg, OD
Laurie Harris, OD
Katherine Heineman, OD
Lee J. Helman, National Cancer Institute (NCI)
Robert Jambou, OD
Robert Lanman, OD
Kathryn Lesh, OD
Cheryl McDonald, OD
Gary Nabel, Vaccine Research Center, NIH
Marina O'Reilly, OD
Michael Pensiero, NIAID
Fran Pollner, *The NIH Catalyst*
Alexander Rakowsky, OD
Eugene Rosenthal, OD
Stuart Z. Shapiro, NIAID
Thomas Shih, OD
Allan Shipp, OD

Others

Approximately 45 individuals attended this 2-day RAC meeting. A list of attendees appears in Attachment II.

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

Dr. Mickelson, RAC Chair, called the meeting to order at 8:30 a.m. on June 14, 2001. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on May 24, 2001 (66 FR 28757). Agenda items included reviews of four gene transfer protocols; the quarterly data management report; discussion of a revised strawman proposed action to amend the *NIH Guidelines* defining the appropriate risk-containment level for a nonvirulent organism; a presentation on Public Health Service (PHS) regulations governing financial conflicts of interest; public discussion of the disposition of individual RAC member comments on protocols that do not require public review; discussion of the exemption in Appendix M-VI-A of the *NIH Guidelines* for certain vaccines; an update on the Final Action to Amend the *NIH Guidelines* relative to the reporting and analysis of serious adverse events; a proposed plan for revisiting the issue of the scope of the *NIH Guidelines*; an update on the planning of an institutional biosafety committee (IBC) policy conference; and an update on the development of GeMCRIS, a national database for gene transfer clinical trials.

Dr. Mickelson reminded the RAC members about the NIH conflict-of-interest policy, which had been provided in written form with the premeeting materials.

A list of abbreviations and acronyms and their meanings appear in Appendix III.

II. Minutes of the March 8, 2001 Meeting/Drs. Gordon and Juengst

Dr. Gordon noted that the entire minutes contained only one misplaced letter. Ms. Levi-Pearl noted that although FDA continues to use the term, "gene therapy", she suggested that the minutes reflect the preferred term, "gene transfer."

A. Committee Motion 1

As moved by Dr. Greenblatt and seconded by Dr. Aguilar-Cordova, the RAC unanimously approved the March 8, 2001 minutes by a vote of 10 in favor, 0 opposed, and 0 abstentions.

III. Discussion of Human Gene Transfer Protocol #0104-469: Subthalamic GAD Gene Transfer in Parkinson's Disease Patients Who Are Candidates for Deep Brain Stimulation

Principal Investigators:	Matthew J. During, M.D., Jefferson Medical College Michael Kaplitt, M.D., Ph.D., New York Hospital and Weill Medical College, Cornell University David Eidelberg, M.D., North Shore University Hospital and Cornell University
Sponsor:	None
RAC Reviewers:	Dr. Breakefield, Ms. King, and Dr. Markert
Ad Hoc Reviewers:	Roy A.E. Bakay, M.D., Ph.D., Rush University and Rush-Presbyterian-St. Luke's Medical Center Howard J. Federoff, M.D., Ph.D., University of Rochester School of Medicine and Dentistry

A. Protocol Summary

This protocol proposes to infuse into the subthalmic nucleus (STN) recombinant adeno-associated virus (AAV) vectors expressing the two isoforms of the enzyme glutamic acid decarboxylase (GAD-65 and GAD-67). The STN, a small region of the brain that plays a central role in the brain's circuitry of cells responsible for regulating movement, is disinhibited in Parkinson's Disease (PD), leading to pathological excitation of its targets, the internal segment of the globus pallidus (Gpi) and substantia nigra pars reticulata (Snpr). Increased Gpi/Snpr outflow is believed responsible for many of the cardinal symptoms of PD, i.e., tremor, rigidity, bradykinesia, and gait disturbance. A large amount of data based on lesioning, electrical stimulation, and local drug infusion studies with gamma-aminobutyric acid (GAMA)-agonists in human PD patients have reinforced this circuit model of PD and the central role of the STN. Moreover, the closest conventional surgical intervention to the proposed protocol, deep brain stimulation (DBS) of the STN, has shown efficacy even in late stage PD. International experience in more than 200 patients has shown that electrical silencing of the STN achieved by DBS results in dramatic improvement in the motor dysfunction seen in PD (of note, there are only partial improvements of voice and speech dysfunctions and minimal improvement in cognitive decline). The investigators believe that the gene transfer strategy will not only palliate symptoms by inhibiting STN activity, as with DBS, but also that the vector converts excitatory STN projections to inhibitory projections. By having the STN become a GABA-producing region (by means of the gene transfer), it is hoped that similar improvements can be achieved.

The preclinical data consist of three models: 1) old chronically lesioned parkinsonian rats in which the intraSTN GAD gene transfer leads not only to improvement in drug-induced asymmetrical behavior, but also in spontaneous behavior; 2) GAD gene transfer preceding the generation of a dopamine lesion where GAD gene transfer showed neuroprotection; 3) in monkeys resistant to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioning in which following GAD transfer, no adverse effects and small improvements in Parkinson rating scales and activity measures were obtained.

The proposed trial design is a double-blind, controlled, phase I trial involving 20 research participants, all of whom will receive DBS and half of whom will receive GAD gene transfer, and half will receive saline into the STN. All DBS patients typically wait several weeks or more for programming and activation of the stimulator; in this clinical trial, they will consent to delay activation of DBS for 6 months, providing an opportunity for the investigators to assess the potential efficacy of the gene transfer.

B. Written Comments From Preliminary Review

All 13 RAC members recommended that the protocol warranted public discussion. Dr. Breakefield, Ms. King, and Dr. Markert were primary reviewers. Drs. Bakay and Federoff were ad hoc reviewers. Reviewers submitted preliminary reviews to which the investigators responded in writing and during this meeting.

Dr. Breakefield noted that this protocol represents the first use of a viral vector for direct administration into the brain of a person with a non-life-threatening disease. Possible vector toxicity is of special concern in a neurodegenerative disease such as PD, as is the targeting of a very small nucleus. There is little leeway for loss of neurons, yet any damage resulting from the volume of the inoculum or the severity of the inflammatory response to virion proteins could cause neuronal loss. An inflammatory response could lead to an autoimmune disease (GAD is the major autoantigen in type-1 diabetes and Stiff-Man syndrome). Dr. Breakefield also requested additional information on 16 items, including which types of neurons and other cell types are present in the STN, issues of neuronal circuitry, whether STN neurons normally respond to GABA, evidence that delivery of GAD to the STN slows degeneration of dopaminergic neurons, the predicted effect of DBS insertion at the time of vector injection on gene delivery to the STN, investigators' plans to monitor generation of antibodies to the STN, and which non-motor-related neurologic and cognitive functions will be monitored in research participants (e.g., GABA agonists can produce memory deficits).

Ms. King's review raised questions about the possibility of transgene overexpression, thus she questioned why investigators believe that GABA overproduction is unlikely to occur or be harmful. She questioned the advisability of linking the gene transfer infusion to the electrode implantation surgery and asked for additional discussion on this point. Regarding the recruitment process, she requested discussion about how investigators will handle the possibility that people with PD may be encouraged to seek DBS surgery to qualify for this study. Ms. King noted the difficulty of commenting meaningfully on the informed consent document because it was submitted to the RAC in rough draft form. However, she provided some suggestions, including rewording the nontechnical abstract, describing the procedure more fully, and restating the potential benefits of this intervention.

Dr. Markert's review centered on immune issues. She noted that antibodies to GAD had not been measured in the animal (monkey) trials. The protocol states that immunohistochemistry is "pending." No nonhuman animal insertion of the DBS was conducted in the preclinical studies, and her concern was that insertion of a foreign body would lead to an inflammatory reaction that might in turn lead to an immune response to GAD. Antigen-presenting cells processing GAD could present peptides, raising concern because the action of GAD peptides on dendritic cells as preventive therapy for diabetes has led to an increased incidence of anaphylactic death in mice. Dr. Markert asked whether the investigators had examined T-cell and B-cell responses to the transferred gene product and suggested adding a statement to the informed consent document that an immune response to GAD could lead to diabetes. Regarding the informed consent document, she suggested that the institutional review board (IRB)-approved document be submitted. The documents submitted to the RAC did not mention how adverse event (AE) reporting will be done and did not discuss the data and safety monitoring board (DSMB), stopping rules, the interval between research participants' enrollment and surgery, and the good clinical practices (GCP) conduct of the trial. Dr. Markert noted that it was difficult to ensure safety when good stopping rules were not discussed in the protocol.

Dr. Bakay's review focused on the clinical study design and preclinical data. Regarding the clinical study design, he noted the lack of safety data on human subjects, a concern about the linkage of this gene transfer study to DBS, the need to identify both target areas before any injection is performed, the untested nature of the proposed rescue procedures, the absence of details in the description of the clinical aspects regarding data entry and management, and concern about how to maintain the study as blinded, the establishment of a DSMB, and designation of a specific end point. Regarding the preclinical data, Dr. Bakay noted that the rodent database is not particularly strong, and that the concern about the potential for causing dystonia should be addressed.

Dr. Federoff raised 22 questions including a request for evidence that excitatory neurons can be converted to inhibitory GABAergic neurons by expression of GAD 65 or 67 and that neurons afferent to the STN will

not be transduced. He also requested data on the different GAD isoforms. In regard to the preclinical research, Dr. Federoff expressed concern about the consequences of delivering two gene products, the lack of knowledge about the compensatory responses of a cell, and the possibility that the proposed protocol may lead to other energy expenditure issues. He also questioned the relevance of the nonhuman animal models to the potential research participant population.

C. RAC Discussion

During RAC discussion of the protocol, several other concerns were raised:

- Dr. Breakefield asked whether the GABA made in the glutamatergic neurons would enter the vesicles and be transported down the long axons to the nerve terminals.

- Dr. Breakefield asked whether there is a nonhuman animal model with a MPTP lesion that is appropriate for PD. She suggested that, if such an animal model exists, efficacy should be evaluated in those animals first before evaluating efficacy in humans.

- Ms. Levi-Pearl offered comments about what should be included in the revised informed consent document, including adding a request for autopsy, the use of lay rather than technical terminology, notation in several places that this is an experiment that is testing for safety only, the addition of subheadings (e.g., risks, benefits, what investigators expect of research participants, what research participants can expect from investigators), an admonition not to sign the form unless all questions have been asked and answered satisfactorily, and financial disclosure information regarding the investigators.

- Even though comments of the ad hoc reviewers were provided orally during the meeting, Dr. Breakefield requested that the investigators respond in writing to the *ad hoc* written reviews.

Ms. King and Ms. Levi-Pearl offered to assist the investigators in revising the informed consent document. Dr. Patterson extended an invitation to the investigators to come back and apprise the RAC of their findings and lessons learned.

D. Investigator Response

Dr. Kaplitt responded to RAC concerns about the protocol's design, specifically the link between the gene transfer infusion and the electrode implantation surgery, by explaining that the rationale behind the initially proposed design was to reduce the surgical risk by combining the procedures. If the gene transfer was successful, the stimulator either would not need to be activated or could be removed; if the gene transfer was not successful, the stimulator could be switched on. Because of the significant concerns expressed by RAC members during the preliminary review, the investigators decided to change the design. Research participants (six research participants will be enrolled) with asymmetrical disease will now be enrolled, and injected unilaterally without concurrently inserting DBS. Omitting the stimulator addresses some of the concerns about confounding variables due to its insertion, as well as any potential side effects from the insertion or from the stimulator itself.

Regarding potential retrograde transport of the virus, Dr. Kaplitt explained that while the striatum is connected to most of the cerebral cortex as well as to many other areas in the brain, the use of the STN is advantageous because its connections are more defined.

Dr. Kaplitt reported that in the event a movement disorder (i.e. dystonia) is induced by released GAD, a traditional subthalamotomy will be performed to lesion the STN or to lesion the area in which the GAD was being released.

Dr. Eidelberg addressed the concerns about the possibility of dystonia. He showed the network modeling relevant to this protocol and explained that a phenotypic conversion to dystonia would involve a network disorder that could be picked up instantly through the proposed network analysis. Dr. Eidelberg asserted that PD conversion to dystonia is rare and not likely to be a major issue for this protocol.

Dr. During reported on new preclinical findings from enzyme-linked immunosorbent assay tests run on primates and rats, which show no detection of GAD antibodies in serum. The data will be submitted to the RAC subsequent to the meeting. Regarding questions about the biology of ectopic expression of GAD and GAD's impact on glutamate, Dr. During acknowledged that debate abounds. Few data have been published, but existing data show no clear consensus. When neurotransmitters are monitored by microdialysis, no change is seen in either glutamate or GABA under the proposed experimental conditions.

In response to Dr. Breakefield's query about GABA transport, Dr. During stated that it is unknown whether the way in which GABA is released matters or not, and which pool releases GABA is not important. GABA is only functional when it acts on GABA-A receptors, to which it does have access; these receptors localize both synaptically and extrasynaptically. He noted that the ultimate goal of this study is to enhance GABAergic tone in a given region of the brain.

In response to Dr. Breakefield's suggestion about additional primate preclinical studies, Dr. During reminded the RAC that the investigators have studied primates primarily in terms of safety and have collected an enormous amount of preclinical data on rodents. The research team did not want to subject more primates to something that ultimately will require human testing.

Dr. During reiterated that the revised protocol is not a double-blind randomized study but will be open label. Six patients, all of whom will have predominantly asymmetric disease, will be enrolled: two patients per dose for three dose levels.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Mickelson summarized the following RAC recommendations, suggestions and comments and acknowledged the investigators' willingness to make the changes suggested during the RAC's public discussion:

- Immunologic parameters should be measured, especially antibody levels to GAD, anti-T-cell, anti-macrophage, and anti-dendritic antibodies should be used in evaluating brain pathology sections in the preclinical models.
- Stopping rules should be defined and included as part of the protocol design.
- Rescue procedures (i.e., what should be done in the event of a severe reaction to the gene transfer product) should be defined and included as part of the protocol design.
- Formal procedures for monitoring and reporting adverse events, both serious and otherwise, should be included as part of the protocol design.
- Deep brain stimulation placement surgery has been eliminated from the protocol design. Therefore, the new procedure that will be utilized to place the gene transfer product into the subthalamic nucleus should be explained in detail.
- Other good clinical practices should be considered and added as appropriate.
- A safety committee (along the lines of a DSMB) should be considered for the evaluation of this study as it progresses.
- Immunologic data from your animal studies (especially from the non-human primate study) should be submitted.
- As an elaboration on the questions raised by Dr. Bakay (an *ad hoc* reviewer), the RAC recommended that a brief discussion be submitted of what animal models would be relevant for this study. The selection of appropriate animal model(s) is especially relevant to proof of concept studies (such as a MPTP lesioned non-human primate study).
- Formal responses to Dr. Federoff's (an *ad hoc* reviewer) and Dr. Bakay's questions and comments should be submitted.
- With regard to the informed consent document, the RAC recommended that the following be added or considered:

- RAC review of a new informed consent document
- Financial disclosure information for all investigators
- A clear delineation of the long-term follow-up that will be needed
- In the event of death, a request for autopsy
- A clearly defined statement that the research participant can drop out of the study at any time without compromising care and that the informed consent document should not be signed until all questions/concerns have been addressed adequately

G. Committee Motion 2

It was moved by Dr. Breakefield and seconded by Dr. Markert that these recommendations expressed the concerns of the RAC and would be included in the letter to the investigators. The vote was 12 in favor, 0 opposed, and 0 abstentions.

IV. Update on Final Action To Amend the Safety Information Reporting Requirements of the *NIH Guidelines*/Dr. Patterson

Dr. Patterson reviewed the four basic elements of the Final Action: (1) harmonization of NIH and FDA requirements, (2) public access to information regarding gene transfer clinical research, (3) safeguarding research participant confidentiality and safety, and (4) establishment of a national gene transfer and safety assessment board. Public comments on this Final Action have concluded, the clearance process is almost complete, and publication of the Final Action in the *Federal Register* is expected soon.

NIH went through an extensive review and consultation process to develop the final action. FDA provided its formal concurrence with the final action which is now undergoing additional steps of administrative clearance. Feedback from the scientific community and others has consistently indicated a strong desire for uniform safety analysis reporting.

Publication of the Final Action in the *Federal Register* will be announced on the OBA Web site; contact will be initiated with key organizations and associations so they can disseminate the Final Action to their constituencies.

V. Proposal To Augment the Membership and Expertise of the NIH RAC/Dr. Patterson

Dr. Patterson provided an overview of the NIH proposal to modify the composition of the RAC. The proposal involves increasing the size of the RAC, enhancing the composition to encompass new areas of expertise, clarifying the description of the RAC's functions, and revising the *NIH Guidelines* so that the RAC's charter is the "controlling document" for the RAC.

The proposed size change would make the number of RAC members more flexible, from the current 15 members plus *ex officios*, to a minimum of 15 and a maximum of 19 voting members plus *ex officios*. Additional proposed expertise would be added from the fields of clinical gene transfer, laboratory safety, and research participant protections. The additional expertise is needed to assist with protocol review and safety assessment due to the increased number of protocols, the expanded scope of clinical indications, and the increased variety of vectors used for gene delivery.

The changes would provide a more accurate description of the current function. Making the RAC charter the controlling document would provide the NIH Director with greater flexibility and the ability to respond more rapidly to scientific developments. It would also clarify the authority of NIH to define the RAC's composition and role. In the *Guidelines* description of the RAC's function, the criteria used to select protocols for public review would be made consistent with the wording in Appendix M.

The next steps are to publish the proposed action for public comment and vote on a final action at a subsequent RAC meeting.

A. RAC Discussion

In response to a question from Dr. Aguilar-Cordova, Dr. Patterson stated that the increase in RAC membership from 15 to 19 would add one additional representative from a nontechnical scientific discipline such as bioethics or law. Three of the additional four members would be drawn from a medical or scientific discipline.

Dr. Macklin suggested adding a RAC member from the science policy field.

Dr. Juengst questioned why it was necessary to state a minimum (15) and maximum (19) number of members. He thought that the new members will likely become permanent members. Dr. Patterson responded that the range allows greater flexibility for the future when the gene transfer field might move clearly in one direction and, therefore, the RAC might possibly need fewer experts.

Dr. Noguchi asked about the Charter being the controlling document of the RAC. Dr. Patterson noted that it is very unusual for the composition and scope of an advisory committee to be set forth in guidelines that require public notice and comment for changes to be made. Generally these are set forth in committee charters and can be modified by the agency as needed to address emerging issues. Dr. Patterson explained that the change in the controlling document is a recognition that emerging issues and new technologies are appearing quickly, and NIH needs to be able to react appropriately by adding expertise to the RAC in a timely fashion.

Dr. Aguilar-Cordova suggested that *ad hoc* reviewers become voting members of the RAC during their presence, which would add expertise at exactly the necessary moment. Dr. Patterson reminded the RAC that voting membership is critical at two junctures: an initial vote for public review and a second vote during the RAC meeting after the protocol has been presented. In order for *ad hoc* members to be voting members of the RAC, they would have to become special government employees and be screened for conflict of interest.

Dr. Macklin suggested that criteria be developed for what would count as "significant," possibly in the form of illustrative examples or a nonexclusive list. Dr. Patterson pointed out that the RAC already has set forth criteria for determining significance, and these are listed in Appendix M of the *NIH Guidelines*. She explained further that the replacement of the term "novel" with "significant" will bring the remainder of the *NIH Guidelines* in line with the terminology used in Appendix M.

B. Committee Motion 3

Dr. Mickelson requested a vote from the RAC in support of putting this proposal into the *Federal Register* to solicit public comments. Dr. Gordon so moved, and Ms. Levi-Pearl seconded the motion. The vote was 12 in favor, 0 opposed, and 0 abstentions.

VI. A Strawman Proposed Action on *E. coli* Risk Group Assessment/Eugene Rosenthal, Ph.D., OBA

RAC Discussants: Drs. Ando and Mickelson
Ad hoc Reviewer: James B. Kaper, Ph.D., University of Maryland School of Medicine

Dr. Rosenthal described the request received by OBA from the University of Florida to define the risk group (RG) status for strain B of the *Escherichia coli (E. coli)* bacterium. Strain B is widely used in industry for large-scale work due to the increased stability of cloned sequences in this strain compared with *E. coli* K-12. At its March 2001 meeting, the RAC considered two criteria necessary for the designation of any strain of *E. coli* as an RG1 agent: (1) that the *E. coli* strain carry deletions in metabolic genes that make it dependent on specialized laboratory media and (2) that it does not present the potential for disease. Because of the problems with large scale production of E. coli, the University of Florida requested that the first criteria be modified to specify deletions that would result in reduced growth rate compared to wild type in complete media.

Dr. Kaper noted that *E. coli* is an important part of the normal flora of the human intestine; however, it can cause urinary tract infections, neonatal meningitis, hemolytic uremic syndrome, diarrhea, and dysentery. Six *E. coli* strains cause diarrhea alone, and *E. coli* causes a wide variety of effects on cells. The pathogenic strains possess a variety of virulence factors encoded on mobile genetic elements that are absent from normal flora or strains chosen for laboratory use.

Strain B has been well characterized in the laboratory. Strain B is a "rough" strain (i.e., it lacks a lipopolysaccharide [LPS] coat), which inhibits its survival in the intestine and the environment. Dr. Kaper stated that he is in favor of the proposal to expand the range of *E. coli* strains in the biosafety level 1 (BSL1) risk group, with provisos about metabolic defects and ensuring the absence of virulent genes.

A. RAC Discussion

Dr. Ando reviewed the differences between BSL1 and BSL2 in large scale production, noting general similarities between the two levels, except that a spill or accident at BSL1 is reported to the local director and spills or accidents in BSL2 are reported to NIH as well as to the local committees.

Dr. Macklin was concerned about the vagueness of the definition of "reduced growth rate", which states that "the strain carries deletion of metabolic genes that result in a reduced growth rate compared to wild type in complete media." Dr. Kaper suggested that, if the criteria must be specified, the specifics should be decided by the local IBC rather than by the RAC; Dr. Mickelson concurred. However, Dr. Noguchi was concerned about potential for different interpretations of the criterion by different IBCs. Dr. Kaper suggested that a useful specific criterion would be that the strains be "rough"—preventing survival in the intestine specifically and in the environment in general.

B. Committee Motion 4

It was proposed that *E. coli* strains that meet the following criteria could be considered as RG1:

- The strain is rough; that is, it does not possess a complete LPS coating.
- The strain does not pose a threat of animal or human disease. It carries neither active virulent factors such as toxins or colonization factors nor genes for these factors.

As moved by Dr. Gordon and seconded by Dr. Aguilar-Cordova, the RAC voted unanimously to approve these two criteria. The vote was 12 in favor, 0 opposed, and 0 abstentions.

VII. GeMCRIS Database Update/Dr. Patterson

Dr. Patterson reported that NIH and FDA are continuing to work together to develop the national gene transfer database called GeMCRIS (Genetic Modification Clinical Research Information System). Phase 1, which consisted of inputting basic information on protocols, including scientific and nontechnical abstracts provided by the principal investigator (PI) or sponsor, has been completed. Phase 2 is under way, with implementation expected in 2002 in a beta-test form available on the Web. It will provide an expanded search engine and analytic capabilities. OBA will continue to gather input on user information and analytic needs.

Dr. Patterson reviewed the overarching goals and objectives of GeMCRIS. The goals are to promote the safe and ethical conduct of gene transfer research, enhance public understanding and awareness of gene transfer clinical research, and maximize the safety of research participants. The objectives are to enhance the analysis and communication of scientific, safety, and outcome information by identifying critical gaps in knowledge and highlighting areas in need of additional research and to facilitate public access to specific clinical trial information.

The database is being designed to accommodate diverse user groups. These include Federal agencies, national advisory committees, local review bodies, policymakers, patients and families, the general public, investigators, sponsors, and the media. A core set of information will be publicly available. As currently

envisioned, a firewall will allow individual clinicians and researchers to see the full set of data for their protocols. The other firewall protects trade secrets and confidential commercial information as required by current law, and will be available only to NIH and FDA.

To gather feedback about the utility of the database design three focus groups were held on June 13, 2001. Two focus groups included scientific and technical representatives, and one group included lay users such as patient, their families and teachers. The focus group moderator is developing a report about user needs, which the database design team will incorporate into its design suggestions and implementation plans. Subsequent consultations regarding user interface and graphics will be conducted.

A. RAC Discussion

Dr. Aguilar-Cordova asked whether the information behind the firewall on this OBA database would be accessible under the Freedom of Information Act (FOIA). Dr. Patterson responded that FOIA is implemented in observance of current statutes that govern confidential commercial information. Therefore, confidential commercial information and trade secrets would not be disclosable under FOIA. Dr. Macklin questioned whether IRB members would have access to information on a particular protocol which is behind the firewall accessible only to investigators and sponsors. Dr. Patterson replied that IRBs or IBCs should already be receiving such information from the investigator or sponsor, thus the need for such access was not clear.

B. Public Comment

Barrie J. Carter, Targeted Genetics Corporation, pointed out that Dr. Patterson introduced this database as the "gene modification" rather than "gene transfer" database. He suggested changing the name of the database to reflect use of the word "transfer". Dr. Breakefield agreed that the use of "transfer" would be more accurate. Dr. Patterson explained that the use of "modification" was an effort to acknowledge that there are other strategies, including organelle transfer, by which modification of the human genome could be achieved. Dr. Noguchi expressed concern that this database, as currently named, might be considered a repository of information or research involving genetically modified foods and nonhuman animals. Dr. Gordon stated that what is in the database and whether it is designed in a retrievable and understandable way is more important than what it is called.

VIII. Conflict of Interest and Research Objectivity: Current NIH Policy/Wendy Baldwin, Ph.D., NIH Office of Extramural Research

Dr. Baldwin was asked to provide an overview of current PHS policies regarding financial conflict of interest (COI). The NIH Office of Extramural Research (OER) developed an Objectivity in Research policy in 1995 to create a framework to address issues that could affect an investigator's objectivity. The Federal rule was developed with the goal of promoting objectivity in the design, conduct, analysis, and reporting of research. All institutions receiving NIH funds must abide by the rule. The rule, which was published in the *NIH Guide* (volume 24, number 25, July 14, 1995) is available at http://grants.nih.gov/grants/guide/notice-files/not95-179.html. Although the rule on Objectivity in Research places the obligation for assessing and managing these issues on the institutions and requires annual reporting to the agency, a recent article in the *New England Journal of Medicine* reported on a survey in which fifteen institutions were found to have no conflict-of-interest policy in place. The OER recently requested major institutions to provide copies of their policies. This summer, the OER will be reviewing the content of each of 300 policies. NIH has the right and the ability to review records. Since minimal reporting may make it easy to overlook problems, OER is reevaluating how the reporting requirements can be managed.

The OER conducted ten proactive compliance site visits in 2000 and is planning to conduct an additional ten proactive site visits this year.

Dr. Baldwin pointed out that human subject protection must be a network of protections. In addition to the IRBs, other components such as DSMBs, NIH oversight, and compliance officers are part of the network. Ensuring a seamless connection among the parts of the network is critical.

A. RAC Discussion

Dr. Breakefield asked about the RAC's role. Dr. Baldwin suggested that the RAC could ask institutions how their compliance offices interact with their IRBs or IBCs in order to gain a better understanding of how the network of protection operates at individual institutions. If the RAC receives an unsatisfactory response, Dr. Baldwin suggested that she be informed so that OER can look into compliance or COI activities at that institution.

Ms. King suggested that the RAC may need to reexamine whether it should require financial COI information within the informed consent document since this requirement may exceed current COI requirements. The RAC could state that each protocol submitted to OBA should include an explanation of how they are complying with their individual institutional policies regarding COI.

Dr. Breakefield asked how FDA interacts with OER's COI regulations. Dr. Noguchi noted that FDA and NIH communicate in regard to inspections. FDA inspection findings are routinely sent to NIH. Dr. Jay Siegel, FDA, clarified that most FDA inspections are conducted to ensure data quality during the drug approval application period rather than to check for financial COI issues.

Dr. Macklin requested that Dr. Baldwin provide some examples of COI situations that are less clear-cut. Dr. Baldwin suggested that she return in December to present a few relevant case studies.

In response to a question from Dr. Mickelson, Dr. Baldwin responded that principles to address institutional COI were being discussed. Concerns have been raised about consistency across different institutions in the approach to this issue. Community-wide agreement on standards is likely to be a more pragmatic and effective way to encourage culture change.

B. Public Comment

Janet Rose Christiansen, Targeted Genetics Corporation, stated that the sponsor can play an integral role in ensuring financial disclosure. Targeted Genetics conducts clinical-site monitoring and does not support investigator investigational new drug applications (INDs). She suggested NIH coordinate its site visits with FDA's inspection visits so that institutions do not face multiple visits within the same short timespan.

IX. Update on the IBC Policy Conference/Allan Shipp, OBA

Mr. Shipp described the upcoming IBC Policy Conference as a forum for exchange of views and the development of consensus on the function of IBCs in today's scientifically dynamic environment. The conference will be the first of several meetings to increase communication between OBA, the RAC and IBCs. A particular focus of the event will be new "nontraditional" forms of IBCs—offsite, central, commercial, and others—that are being proposed and formed. A central question is whether these novel types of review committees can fulfill the IBC roles and responsibilities defined in the *NIH Guidelines*. With this consideration in mind, a roundtable of experts will be asked to make specific recommendations for OBA policy and possible modification of the *NIH Guidelines.*

Initial sessions will provide a historical perspective on IBCs and their current function. Other presentations will focus on the environment in which IBCs operate relative to new directions in science, such as the increase in multisite trials. The 1½-day conference will start with a general overview and statement of the problem and then offer presentations about how IBCs are formed and how they function, followed by a roundtable discussion with selected experts—investigators, patients, industry representative —to deal with specific policy questions.

The IBC Policy Conference is tentatively titled "IBCs in a Changing Landscape: A Policy Conference" and is scheduled tentatively for Friday, December 7 (full day), and Saturday, December 8 (half day), to coincide with the December 2001 RAC meeting. The location of the conference will be announced later.

The IBC Policy Conference will focus on OBA policy concerns. A professional development conference for the IBC community might be helpful at some future date.

A. RAC Discussion

Dr. Markert suggested adding the issue of the effectiveness of IBCs. This issue could be addressed by OBA staff members by interviewing IBC chairs anonymously and reporting on what the chairs view as their contribution.

Mr. Shipp stated that the University of North Carolina (UNC) will be conducting a survey to look at the scope of IBC activities and interactions at the host institution. Ms. King added that the UNC IBC administrator discussed IBCs at the most recent national IBC meeting and found that these committees differ across the country. The UNC IBC administrator is interested in sponsoring a survey to find out how different IBCs work, and he asked Ms. King to ask the RAC whether the results of this survey should be made generally available. Ms. King asked whether the results could be disseminated at the December 2001 IBC Policy Conference. Dr. Mickelson responded that the RAC is definitely interested in the survey's results, but that they do not have to be available by December 2001. Mr. Shipp added that the IBC Policy Conference is likely to result in an enumeration of the characteristics expected of IBCs, the nature of IBC review, and the kinds of criteria to apply in evaluating the acceptability of nontraditional IBC arrangements and whether those arrangements meet expectations. A survey of the kind suggested by Ms. King might help inform those results.

Mr. Shipp reported that he has been in contact with Public Responsibility in Medicine and Research, the national IRB organization, about the December 2001 conference, with the hope of including content specific to how IBCs interact with IRBs and related issues.

X. Communication of Issues Raised by Individual RAC Members Following the Preliminary RAC Review of Human Gene Transfer Protocols/Ms. King

Ms. King presented a proposal to convey comments to PIs, IBCs, and IRBs from individual RAC members on preliminary review of protocols that were exempted from in-depth RAC review and public discussion.

The goal for this change would be to enable IRBs, IBCs, investigators, and sponsors to engage in more productive discussions about gene transfer protocols at the local level. The potential utility of these comments to local oversight bodies increased following the October 10, 2000 change to the *NIH Guidelines* that required RAC review prior to final IBC approval and, possibly, IRB approval. Most protocols (70 to 85 percent) are exempted from in-depth RAC review and public discussion. Two major issues would need to be considered: (1) whether sharing individual comments is consistent with the role of the RAC as a Federal advisory committee and (2) how the comments should be conveyed.

The proposed text for the exemption letter would read:

> "As you know, during the preliminary protocol review process, individual RAC members may request additional information or clarification about your protocol and sometimes make specific comments or suggestions about the protocol design, informed consent document, or other matters. Individual RAC member comments are then conveyed to you for response. *[Option #1: A copy of those exchanges is attached for your records and for the benefit of your IRB and IBC as they review the protocol.] [Option #2: A copy of those exchanges may be obtained from the NIH Office of Biotechnology Activities.]* It is important to emphasize that these comments do not necessarily represent a consensus of the RAC; they are advisory only and, like those that emerge from the public review process, are not binding. Nonetheless, comments by RAC members are considered carefully and may be of use during local review; we hope that this input will be shared by all concerned at your institution."

Ms. King proposed two ways to accomplish this sharing of information: OBA can (1) gather the e-mail correspondence about a protocol and attach it to the exemption letter, making it routinely available, or (2) state that these comments are available and how to request them. This change would not require an amendment to the *NIH Guidelines*. However, RAC members would need to be mindful of the public nature of e-mail correspondence, and there would be an increased workload for OBA staff.

A. RAC Discussion

In response to a question from Dr. Ando, Ms. King explained that PIs already receive copies of RAC members' questions through OBA, but that those comments also should be available routinely to IRBs and IBCs directly from OBA.

Dr. Gordon asked whether a member of the public currently could obtain access to an e-mail message sent to an investigator through OBA. For all general e-mails sent to OBA, Dr. Patterson responded that OBA would evaluate the request and the nature of the e-mail exchange. However, the e-mail message probably would be releasable under FOIA. RAC members' e-mail messages intended to be communicated to the PI or sponsor through OBA become part of the protocol record and would be publicly accessible without use of FOIA.

Dr. Markert expressed her concern about e-mail comments from RAC members who may know little about the specific topic and are merely looking for clarification from the PI or sponsor. It would be helpful for IBCs and IRBs to have a general idea of the expertise of the person asking the question. Ms. King noted that current practice makes these e-mail comments part of the official record of each protocol and this proposal would only make it easier for local review boards to access those comments. The proposed change also would provide an additional impetus for RAC members' comments to be especially clear, since they might be read by local review boards as well as a broader audience of PIs.

Dr. Gordon expressed two concerns. First IRBs that are "in the dark" about gene transfer would still be in the dark about how to handle some of the RAC e-mail comments. Those boards would likely deal with the comments by returning them to the PI for action. Second the broader sharing of the comments might inhibit RAC members who do not want to appear naive. He explained that, when he communicates with investigators about diseases about which he is not an expert, he tries to edify himself while communicating with the PI, and he feels free to express ignorance. Ms. King explained her view that the RAC's role as an advisor to PIs, sponsors, and the public is perfectly compatible with an advisory role for IRBs and IBCs during their local review process, and that the potential benefits of the proposal outweigh the potential risks.

Dr. Breakefield commented on the importance of minority opinions and the value of the review process in ensuring that all questions, even those raised by only one member are addressed. Dr. Aguilar-Cordova concurred, stating that RAC members spend time reviewing a protocol and making comments about it and local review boards could benefit from the perspectives they have gained.

Dr. Mickelson stated that the proposal would cause her to be somewhat more circumspect and endeavor to be clear about her lack of understanding of a concept or issue, but that additional carefulness might have a positive effect.

Ms. Levi-Pearl expressed her support for the proposal, especially given that most protocols do not receive public review by the RAC. The additional information would be valuable for IRBs and IBCs. Ms. Levi-Pearl also noted that the RAC should make every effort to ensure improved thinking and careful consideration of each protocol. The proposed change would help accomplish that goal.

Dr. Gordon commented that communications from the RAC could have a negative impact if they were misunderstood, in part because IRBs and IBCs may have the incorrect view that the RAC is a regulatory body. Ms. King expressed her belief that it is the RAC's job to make its role clear, especially if that role differs from the general perception. Dr. Gordon reiterated that he did not want to inadvertently exert influence on protocols not requiring full public review by the RAC. He expressed concern about the perception of the RAC as a regulatory body and that RAC members do not have the expertise to micromanage most of the protocols that come before it.

Dr. Ando reported on information he gleaned from a recent meeting regarding the liability of IRBs and noted that statements from the RAC are used in liability cases.

With regard to Dr. Gordon's concerns, Dr. Mickelson suggested that one option would be to allow RAC members to opt out of having their comments included in the exemption letter to the PI, which would also

be sent to the IRB and the IBC.

B. Public Comment

Ms. Christensen, Targeted Genetics, asked whether RAC members expect responses to their individual comments, in part because of concerns about delaying the protocol approval process. Ms. King responded that these questions have already been answered, and OBA would be providing to the local review boards both the questions and the answers, a record of the exchanges that should expand the boards' understanding of the protocols and make their deliberations easier.

Ms. Christensen related an experience in which an IBC would not permit the sponsor to move forward with the protocol until every single point in the post-RAC meeting letter to the PI was addressed, even though some of those points were only suggestions. She suggested that OBA clarify the context in which this information is provided to IRBs and IBCs so local review boards know how to weigh the information they receive. Ms. King responded that there is a difference between the recommendations arrived at by consensus during full public review and individual comments made before that review. This difference would be made clear.

J. Tyler Martin, Sr., Valentis, commented that the current mechanism for feedback to local review boards (the exemption letter) addresses the issue being discussed. Valentis' experience indicates that any RAC comment included in the exemption letter becomes a statutory obligation in the IRBs' or IBCs' hands. In the current environment, local review committees are unwilling to ignore a comment, no matter how peripheral it is.

Dr. W. French Anderson, University of Southern California, supported Mr. Martin's contention. A protocol of his was recently reviewed by the RAC, and his IRB tabled the protocol until absolutely everything listed in the RAC letter had been accomplished.

Jeffrey M. Ostrove, Ceregene, related his IRB requested a second letter from OBA stating that every comment and question asked of the PI was satisfied. This experience points out that IRBs are truly concerned about and attentive to the outcome of RAC review.

Diane O. Fleming, a certified biosafety consultant, commented that multicenter trials pose a particular challenge in communicating questions and concerns from the RAC, and she expressed hope that PIs and sponsors would be encouraged to share that information.

C. Vote of the Committee

Ms. King moved and Ms. Levi-Pearl seconded the agreement with the intent of making available to IRBs and IBCs the RAC member's comments and exchanges with PIs on exempt protocols. The vote was 9 in favor, 2 opposed, and 1 abstention.

D. Postponement of Additional Discussion

Dr. Mickelson requested that additional action (i.e., a determination of the method of making the information available) on this issue be postponed until the September 2001 RAC meeting because of time considerations.

XI. Discussion of Human Gene Transfer Protocol #0104-470: A Phase I/II Dose-Escalation and Activity Study of Intravenous Injections of OCaP1 in Subjects With Refractory Osteosarcoma Metastatic to Lung

Principal Investigators:	Paul A. Meyers, M.D., Memorial Sloan-Kettering Cancer Center Michael J. Hawkins, M.D., Washington Hospital Center
Sponsor:	DirectGene, Inc., represented by Dale VanderPutten, Ph.D., M.B.A. Lee J. Helman, M.D., NCI
RAC Reviewers:	Dr. Chow, Ms. King, and Dr. Markert

A. Protocol Summary

Osteosarcomas, a type of bone cancer also referred to as osteogenic sarcomas, are cancers that occur most frequently during childhood and adolescence and were once fatal in more than 80 percent of patients. Chemotherapy, better surgical techniques, and improved staging methods now allow most patients to be treated without amputation and to be cured of their disease. However, many patients are not cured and die when their cancer spreads to vital organs such as the lungs. The lung is the most frequent site of tumor spread and is treated with chemotherapy and surgical resections. Often, multiple lung surgeries are required for tumors that continue to reappear in the lung. Eventually, more surgery can no longer be done because either too much lung tissue has been removed or the surgery has become futile because more tumors reappear quickly. Although chemotherapy is a main component of initial therapy, it has not been shown to be of benefit for recurrent disease.

This trial uses an adenovirus, called Ad-OC-E1a, to specifically target and kill bone cancer that has spread to the lungs. The virus is able to replicate only in bone cancer cells because it is controlled by the osteocalcin (OC) promoter OCaP—which regulates transcription only in cells that have the ability to deposit calcium, such as some normal bone cells and bone cancer. Normally, the osteocalcin promoter is primarily active during development, when bones are growing. Bone cancer cells have properties similar to normal bone cells, and often retain these properties even if they have spread to other sites, such as the lung. Therefore, this study hopes to demonstrate the ability of Ad-OC-E1a to safely target and kill bone cancer cells by using a cancer-specific control element (OCaP1) that prevents the spread of the virus to normal tissues with the exception of some bone cells while allowing it to remain active in cancer cells. To minimize spread of the virus to bone cells, the Ad-OC-E1a virus will be given intravenously allowing for a primary pass through the pulmonary system where the virus should be taken up actively.

This trial will study Ad-OC-E1a for the treatment of metastatic cancer that can no longer be cured with chemotherapy. In the first part of the study, research participants will receive a single intravenous (IV) injection with one of four doses of Ad-OC-E1a. Once safety is established in this part of the study, the researchers then will determine the antitumor activity of Ad-OC-E1a in research participants with bone cancer that has spread to the lungs and for whom an operation to remove the lung tumors is indicated as part of their standard care. To determine whether Ad-OC-E1a is active in these individuals, they will undergo serial computerized tomography scans of the lung tumors not operated upon and pathologic examination of the tumors that are surgically removed.

B. Written Comments From Preliminary Review

This protocol was selected for public review by three RAC members. Dr. Chow, Ms. King, and Dr. Markert submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Chow's major concerns centered around the enrollment of research participants younger than 18 years old and the preclinical toxicity studies that have yet to be completed. She suggested studies in young rodents to investigate OC expression patterns, the pattern of possible viral replication in bones and other organs, and the short- and long-term effects of IV injection of this virus on bone integrity, growth, and strength. Dr. Chow also suggested that the Phase I safety study be conducted in research participants age 18 or older while the young rodent studies are being carried out. When the preclinical safety data demonstrate acceptable toxicity and the virus proves safe in adult research participants, the protocol could then be amended to include research participants younger than 18 years of age.

Ms. King's review centered on the enrollment of research participants in the 13- to 17-year-old age range. She did not consider the scanty evidence of *in vitro* and rodent studies as a sufficient basis for asserting the potential for direct benefit to the first human subjects in a dose-escalation study, and she stated her preference that enrollment of minors be deferred until the second part of the study. Regarding the draft informed consent document, Ms. King suggested that the investigators prepare an assent form for enrolled minors, produce separate informed consent documents for parts 1 and 2 of the trial, and not use terms such as "therapy" and "treatment," which imply benefit. She also suggested that the informed consent document be revised—before enrollment in part 2 of the trial—to include safety and risk information learned from part 1.

Dr. Markert's concerns centered on researchers' expectations of AEs, especially several grade 3 AEs, and the lack of information about the DSMB and reporting to OBA. She asked whether virus is found in semen. She suggested mice at weaning (3 weeks old) could be reasonable models for human children. Despite the potential for AEs at bone growth plates and other concerns, she stated her support for the enrollment of children as young as 13 years old because despite having received chemotherapy and often surgery, these children have a grim prognosis. By participating in this research, they may help others with this type of tumor.

C. RAC Discussion

Dr. Aguilar-Cordova suggested that the *in vitro* studies be done comparing this adenovirus with wild-type virus to determine the level of attentuation with the engineered promoter. He expressed concern that the applicability of the toxicology studies is only to the acute phase, in which some toxicity was seen. This finding is compounded by the fact that human adenoviruses do not replicate in murine cells. Dr. Aguilar-Cordova also expressed concern that there were no studies of preimmunized nonhuman animals that would monitor the transduction occurring in the presence of neutralizing antibodies to adenoviruses. He asked whether the investigators considered injecting this virus intralesionally rather than using systemic delivery.

Dr. Breakefield was concerned that it is not known how the promoter will behave in younger individuals. The promoter does not replicate well in rodents making it difficult to model for humans. The adult rat models used to date do not have tumors and do not have growing bones. She suggested using younger rats and maximizing virus replication to check for unanticipated results.

Dr. Ando asked about the median survival rate and general growth status of individuals with this disease. Because of the small amount of virus seen in urine two weeks post-infusion in the animal models, Dr. Ando recommended that excretion of viral particles be monitored for longer than presently proposed in the protocol.

Dr. Gordon requested that investigators comment on whether microscopic metastases over a large surface area can be accessed with the proposed dose. He also requested comment on conducting this gene transfer on someone who has already had chemotherapy, who might be less likely to respond well and who might be immunocompromised.

Ms. King suggested that investigators enroll in part 1 of this clinical trial only research participants who can give their own consent.

Dr. Breakefield commented that the biggest risk to children might be that the virus would start replicating in the lung and would cause extensive lung damage. She suggested an experiment in which the investigators administer the virus intravenously to adult and young rats with metastatic osteosarcoma to the lung to see what kind of lung damage occurs, if any.

Dr. Gordon noted that the age group in question has so much to lose in years of life that the possibility of extending their lives and significantly reducing morbidity would inspire hope.

Ms. King recommended that the investigators consider using a consent monitor for research participants who are 13 to 17 years old to ensure that these children understand the research-related issues and are making decisions of their own free will. Dr. Macklin supported this recommendation.

Ms. Levi-Pearl stated that the informed consent document for part 1 of this trial was one of the best forms she had ever seen and that she intends to use it as a model.

RAC members appreciated that this PI and sponsor were conducting research on a small patient population that normally does not receive much experimental treatment.

D. Investigator Response

Dr. Hawkins stated that the investigators would agree to collect samples to look retrospectively at potential cytokines. Although he was not opposed to an outside group reviewing the toxicity data for this study, he explained that, if this product proved to be toxic, the sponsor would stop the study long before a DSMB sees the data. Regarding the potential for therapeutic effect, Dr. Hawkins commented that one specific nonhuman animal model of osteogenic sarcoma with pulmonary metastases showed activity with the OC restriction. Dr. Hawkins agreed that Dr. Breakefield's suggested experiment with rats with metastatic osteosarcoma to the lung would be relatively easy to conduct. He explained that intralesional injection was considered but rejected because no potential therapeutic benefit was posited—injecting this material into a single isolated lesion would offer the research participant no opportunity for benefit, merely risk.

Dr. Meyers explained that there are approximately 600 cases of osteosarcoma diagnosed each year in the United States. Using the best therapy, about 70 percent of those patients will have long-term, event-free survival as a result of their initial therapy. The median time to the first failure is 18 months; of the 600 patients, 30 percent (180 patients) will develop recurrent osteosarcoma each year. Virtually all of those recurrences will occur in the lung, and these patients would be potential candidates for this type of approach. From the time of first pulmonary recurrence, median survival thereafter is about 9 months, and the median time until a second recurrence is 5 months. These patients have a very short life expectancy.

In answer to the question about the nature of growth in young patients who have been treated primarily for osteosarcoma, Dr. Meyers responded that, typically, their adult height is slightly less than would be expected. The chemotherapy has some effects on nutrition, and these tumors often arise in the lower extremities. Thus there is some loss of growth in limbs, but since these patients tend to be taller than normal at time of diagnosis, this small loss of height results in average adult height.

Regarding the question about the degree of immunosuppression in these potential research participants and whether they are likely to be at greater risk when receiving a replication-competent virus, Dr. Meyers did not believe there was much detailed information about the immune status of patients who have been treated for osteosarcoma. However, he expected that most of these patients are relatively immunocompetent at the time they would be eligible for trials of this type.

Dr. Meyers also responded to RAC members' comments about the prospect for clinical benefit and how that affects the enrollment of research participants. Phase I studies in pediatric populations are problematic, but the investigators' philosophy is to carry out pediatric Phase I trials using only agents that have a reasonable expectation of benefit, even though that criterion might not be represented as the principal purpose of the clinical trial. Dr. Helman noted that unexpected toxicity is a concept struggled with daily by people who work with children afflicted with serious illnesses.

Dr. VanderPutten discussed the tissue specificity of the OC promoter and the relative OC-controlled expression of genes on the basis of tissue specificity. He stated that liver findings in toxicology studies indicate some level of liver toxicity associated with high doses of adenovirus (not an unexpected finding). In addition, there is no evidence for replication in rodents, although the investigators will continue to search for evidence of replication.

With respect to obtaining assent from child research participants, Dr. Helman explained that it is very difficult to treat a child on any investigational study without assent, because the child will refuse therapy. Children who are hesitant about participating would never enter a study, even if the parents were enthusiastic.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Mickelson summarized the following RAC recommendations:

With regard to the clinical protocol:

- It was agreed that pediatric patients age 13 and older could be enrolled into the first part of the study, as proposed in the protocol.

- The investigator agreed to monitor for the presence of virus for a longer period of time than proposed in the protocol, though the details of the exact time frame were not discussed.

- The investigator agreed to list grade II nausea and vomiting, grade III transaminase elevations, grade III neutropenia, and grade III thrombocytopenia as unexpected adverse events rather than as expected as listed in the protocol.

- The investigator agreed to collect extra vials of blood and to store them for potential use (such as monitoring cytokine levels, if needed).

- It was suggested that the investigator utilize an outside monitor for this study. This could be an attending physician from one of the participating institutions who would understand the science behind the protocol, but who would not be directly involved with it.

With regard to the informed consent document:

- It was recommended that a separate document be written for each of the two components of the study.

- It was recommended that a consent monitor be used when enrolling subjects in the 13-17 year age range.

- The RAC extended an invitation to the investigator to submit the new informed consent document for review.

With regard to the pre-clinical studies:

- The investigators were encouraged to continue to assess adenovirus replication in rats at high doses to determine if the configuration of their vector changes the propagation kinetics of the virus such that it is capable of replication in rat tissues, an indication of its altered tropism.

- The investigators agreed to complete a study in pubertal rats (circa 35 days old) during active bone growth to evaluate potential toxicity.

- It was recommended that an additional study be done where the vector is used in rats with established osteosarcoma lung metastases, ideally immunocompromised rats with human osteosarcoma cells to assess potential toxicity to lung tissue at sites of active viral replication as well as systemic toxicity and virus propagation. This study would also be useful for demonstrating potential efficacy.

G. Committee Motion 5

It was moved by Dr. Gordon and seconded by Dr. Aguilar-Cordova that the recommendations expressed the concerns of the RAC. The vote was 12 in favor, 0 opposed, and 0 abstentions.

XII. Day One Adjournment/Dr. Mickelson

Dr. Mickelson thanked the participants and adjourned the first day of the June 2001 RAC meeting at 6:25 p.m. on June 14, 2001.

XIII. Day Two Opening Remarks/Dr. Mickelson

Dr. Mickelson opened the second day of the June 2001 RAC meeting at 8:30 a.m. on June 15, 2001.

XIV. Discussion of Human Gene Transfer Protocol #0104-462: A Phase I Trial of Genetically Modified *Salmonella typhimurium* Expressing Cytosine Deaminase (TAPET-CD, VNP20029) Administered by Intratumoral Injection in Combination With 5-Fluorocytosine for Patients With Advanced or Metastatic Cancer

Principal Investigators:	John J. Nemunaitis, M.D., and Charles Cunningham, M.D., Mary Crowley Medical Research Center (U.S. Oncology)
Sponsor:	Vion Pharmaceuticals, Inc., represented by Ivan King, Ph.D.; King Lee, Ph.D., R.A.C.; and Mario Sznol, M.D.
RAC Reviewers:	Drs. Ando, Macklin, and Mickelson
Ad hoc Reviewer:	Carol O. Tacket, M.D., University of Maryland School of Medicine

A. Protocol Summary

One approach to improving the treatment of cancer is to deliver most of the anticancer agent directly to the tumor, thus concentrating the effect on the tumor and avoiding toxicity to normal tissue. Some bacteria accumulate preferentially within tumors following IV or direct tumor injection in animals, reaching very high numbers in the tumor compared with normal tissue. Thus, bacteria could be used to deliver anticancer agents to tumors if they could be administered without causing serious consequences of infection, such as damage to normal organs and, in severe cases, septic shock and death.

The investigators have modified a type of *Salmonella* bacteria by taking out two genes. The bacteria was attentuated by a partial deletion of the msbB gene responsible for addition of a terminal myristyl group to lipid A. Lipopolysaccharide derived from these lipid A mutants had a markedly diminished ability to induce tumor necrosis factor in human monocytes and in vivo mouse models. The bacteria,VNP20009, was further attenuated by deletions in the purI gene, creating a requirement for an external source of purines. The mutations were accomplished by deletions of large portions of the genes, making reversion to wild type highly unlikely. The genetic characteristics of the attenuated bacteria were shown to be stable for more than 150 generations.

VNP20009 can be given safely at high doses to mice with implanted tumors, by the IV route or by direct injection into the tumor. These bacteria retain their property of preferentially accumulating within the tumors. On the basis of this information, the investigators started human clinical trials of VNP20009. In one of those trials, the investigators showed that VNP20009 can be injected directly into tumors, and to date, only minimal side effects have occurred. VNP20009 persists in the tumor for at least 2 weeks in most research participants, and VNP20009 bacteria are not shed from the body in stool or urine, which indicates that these bacteria are unlikely to spread to health care workers or others.

VNP20009 has been further modified by insertion of an E. coli cytosine deaminase (CD) gene which when expressed converts 5-fluorcytosine (5-FC) to 5-fluorouracil (5-FU). The CD containing VNP20009 was designated TAPET-CD or VNP20029. In terms of toxicity and ability to accumulate preferentially in tumor, TAPET-CD behaves similarly to VNP20009 in animal models. When the prodrug 5-FC is given (in mice into the abdominal cavity where it is absorbed into the blood), it circulates within the body. It then is converted to the more toxic drug 5-FU in the tumor but not in other parts of the body because of the preferential accumulation of TAPET-CD (and therefore, CD) in the tumor. The 5-FU that is produced locally within the tumor can kill tumor cells. The combination of the TAPET-CD bacteria and 5-FC was found to be safe in nonhuman animal models and to produce tumor-growth inhibition; in some cases, it caused tumor shrinkage.

On the basis of the nonhuman animal model information, this clinical study proposes to test the combination of TAPET-CD and 5-FC in research participants with advanced cancer who have exhausted all other effective treatment options. The bacteria will be injected directly into a tumor. After 3 days, the

drug 5-FC will be given by mouth three times per day for 14 days. If the tumor shows signs of stabilization or shrinkage and if other tumors in the body are not growing, the cycle of bacterial injection and 5-FC treatment will be repeated every 28 days.

B. Written Comments From Preliminary Review

This protocol was selected for public review by seven RAC members. Drs. Ando, Macklin, and Mickelson submitted written reviews, as did *ad hoc* reviewer Dr. Tacket, to which the investigators responded in writing and during this meeting.

Dr. Ando's major concern was the novel approach proposed involving a pathogenic bacterium to provide an enzyme that will convert to chemotherapy and increase local concentration. He wondered about the long-term consequences of *Salmonella* infection in humans and how that would be monitored. Long-term consequences might include disabling chronic bone infections or a systemic infection. Dr. Ando also suggested that the investigators' use of urine and stool cultures (to assess gastrointestinal colonization) may not be sensitive enough and that they should consider looking for chronic shedding using a more sensitive technique such as polymerase chain reaction (PCR).

In her review, Dr. Macklin commented on four ethical aspects of the protocol: (1) risk-benefit assessment, (2) recruitment of research participants, (3) the informed consent process and document, and (4) monetary costs to research participants. She noted that it is difficult to make a risk-benefit assessment of this protocol because it is the first use of TAPET-CD in humans. The intervention is expected to be palliative and not curative because the research participants have advanced metastatic cancer and have exhausted other treatments available to them. Dr. Macklin queried whether the investigators or the individuals' personal physicians would recruit the research participants. She stated that the informed consent document is too long and is written at a reading level significantly higher than that required by Appendix M (i.e., "eighth grade education"). Dr. Macklin also suggested additional wording changes in the document, including deletion of the section "relinquishment of property rights." She also stated that the monetary costs to research participants should be delineated.

Dr. Mickelson's major concern related to the novelty of the gene delivery agent and its potential use in cancer therapy. Her questions included whether there is any expectation that *Salmonella* will reach the brain, whether any leakage of bacteria from the tumors into the general circulation could be expected, and whether there is any evidence of loss of culture homogeneity over time with such high-dose levels of TAPET-CD. Other concerns were the possibility of a greater intensity or duration of adverse events (since these research participants may have weakened immune systems), adequate monitoring of the side effects of agent administration, and the inadequacy of the materials (given to research participants) that outline the precautions for prevention of transmission of the bacterial agent to others.

Dr. Tacket noted that, after intratumoral injections, at least one research participant had drainage from the wound for several weeks; investigators should make certain that research participants know how to change dressings. She also wanted more information about clinical histories and outcomes for research participants who received the parent vector (VNP20009), the timing of administration of 5-FC and *Salmonella*, which antibody responses the investigators were looking for, and how the mutation in lipid A (the biologically active component of lipopolysaccharides that shows strong endotoxic activity and exhibits immunologic properties) will affect identification of the organisms by serology after culture.

C. RAC Discussion

Dr. Aguilar-Cordova noted that the investigators reported thrombocytopenia as one of the dose-limiting toxicities on their first trial, and 5-FU might also have some thrombocytopenia side effects. He queried whether the investigators, in their nonhuman animal studies, had seen any additive toxicity effects as well as the additive efficacy effects mentioned.

Dr. Gordon asked whether the investigators had conducted intracranial injections of bacteria in nonhuman animals, followed by treating or not treating for the bacteria. Specifically, he suggested injecting 100,000 bacteria into the brains of mice and following that injection with antibiotic treatment to show that the bacteria could be eliminated quickly and easily.

Ms. Levi-Pearl noted the absence of financial disclosure information in the informed consent document.

D. Investigator Response

Commenting on the use of culture vs. PCR in detecting the vector and vector shedding, Dr. Lee stated that PCR could be problematic for analyzing bacteria in urine and fecal samples because bacteria cannot survive in stool and is difficult to detect in urine. PCR may be a good way to detect continued shedding, but when looking for the possibility of transmission to other humans or to other animals, the culturing method proposed by the investigators is superior to PCR.

Regarding the worst-case possibility that permanent colonization would occur, Dr. Lee explained that every patient who comes off study receives an intensive course of antibiotics for 2 weeks, even if no bacteria are detected. These research participants will be difficult to follow over the long term because they are advanced cancer patients. To date, the investigators have found no chronic or persistent bacterial infection.

Dr. Sznol agreed to make every change in the informed consent document suggested by Dr. Macklin, with the exception of the use of 5-FC in this setting being investigational, not standard care.

The purpose of the companion accompanying the research participant after discharge from the outpatient clinic was discussed by Dr. Sznol. At the request of the investigators and on the basis of the safety data generated with the base vector, research participants will be treated in a well-monitored outpatient clinic. They can be discharged from that clinic 8 to 12 hours after administration if they have less than grade 1 toxicity. Only then will they be allowed to go to a hotel that is on the Baylor University campus and within 400 yards of the hospital and emergency room. The companion will act in situations in which the research participant cannot get back to the clinic alone.

Dr. Sznol responded to Dr. Aguilar-Cordova's query about additive toxicity effects. At very high doses of both agents (5-FC and 5-FU), some cumulative toxicity was seen but not myelosuppression.

Dr. Sznol responded to Dr. Gordon's question about intracranial injections in nonhuman animals by stating that distribution studies in mice showed some bacteria in the brain. It was not known whether this was an accurate finding. Dr. Lee noted that larger animals (e.g., dog and monkey) are more relevant to humans, and no bacteria have been found in the brains of these larger animals. Dr. Sznol explained that the investigators will exclude research participants who have brain metastases. In response to Dr. Gordon's suggestion of injecting bacteria into the mouse brain and then treating with antibiotics, Dr. Sznol agreed that this experiment would be worth conducting and agreed to do so.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Mickelson summarized the following RAC concerns and recommendations:

- The long-term consequences of *Salmonella* infection need to be studied.
- The investigators will consider looking for a consistent (surrogate) marker for possible colonization of replicating (possibly pathogenic) organisms.
- The detection of vector in the brains of mice warrants a nonhuman animal experiment consisting of intracranial injection of vector followed by antibiotic treatment; investigators agreed to conduct such a study.
- The investigators agreed with Dr. Macklin's suggestions regarding ethical issues.
- Financial disclosure information will be included.

- The investigators will clarify any costs that research participants might incur.

- "Relinquishment of property rights" will be clarified or removed from the informed consent document.

G. Committee Motion 6

It was moved by Dr. Macklin and seconded by Dr. Juengst that the recommendations expressed the concerns of the RAC. The vote was 12 in favor, 0 opposed, and 0 abstentions.

XV. Discussion of Appendix M-VI-A on Vaccine Exemption From OBA Registration and RAC Submission: Interpreting the Clause "persistence of the vector-encoded immunogen"

RAC Discussants:	Drs. Aguilar-Cordova and Breakefield
Ad hoc Discussants:	Neal DeLuca, Ph.D., University of Pittsburgh
	Karen Midthun, M.D., Center for Biologics Evaluation and Research (CBER), FDA
	Gary Nabel, M.D., Ph.D., Vaccine Research Center, NIH
	Michael Pensiero, Ph.D., NIAID
	Stephanie L. Simek, Ph.D., CBER, FDA

Dr. Patterson provided the background regarding Appendix M-VI-A. Vaccines for infectious diseases can be highly similar to gene transfer vectors used for other clinical purposes and may even express some of the same genes. Such vaccines have been exempted from RAC review if they meet the criteria set forth in Appendix M VI-A of the *NIH Guidelines*: "Human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector encoded immunogen is not expected, are exempt from Appendix M-I, Submission requirements, and Appendix M-I-C, Reporting requirements-Human Gene Transfer Experiments." Vaccine protocols proposing the use of vector expression systems capable of sustaining transgene expression for several months have prompted considerable discussion among RAC members and institutional officials and have raised the question of how to interpret and apply the "persistence" clause of Appendix M VI-A. The main issue for today's discussion should be the interpretation of "persistence of vector-encoded immunogen" to ensure that protocols requiring RAC attention are appropriately identified. A longer term issue would be whether or not the overall purpose and scientific basis of the exemption need to be re-examined.

To focus the discussion on the "persistence" criteria, Dr. Patterson suggested the following the questions:

- What observations and findings regarding the persistence of vector-encoded immunogens have been generated from gene transfer vaccine studies to date? What have been the clinical consequences, if any, of persistent immunogen in these settings? What are the factors that govern persistence of the vector-encoded immunogen—immunogen half-life, immunogen bioactivity or mechanism of action, vector expression system half-life, route of vector administration, or other factors?

- How should the phrase "persistence of the vector-encoded immunogen" be interpreted by the NIH and local committees to ensure that protocols are referred to the RAC for review as appropriate? For example, does this refer to detectible transgene product in plasma as well as in other tissues such as lymph node or liver? Does the transgene product need to be intact, or are residual metabolites or protein fragments considered as "persistence of the vector-encoded immunogen"?

- How should nonpersistence of the immunogen be used as a criterion, or should it be used as a criterion for exemption from RAC review?

- Should gene transfer vaccine protocols using the following not be exempted from RAC review and data reporting: vectors capable of long-term transgene expression (What is long-term expression?) and vectors capable of stable integration into the human genome? Should the

current exemption be clarified?

Dr. Patterson stated that OBA and NIH look forward to insights and guidance in setting forth a clear, consistent, and logical set of criteria to determine which protocols should be reviewed by the RAC.

Dr. Midthun provided an overview of FDA's Office of Vaccine Research and Review (OVRR) approach to viral vaccines. Types of viral vaccines include both classical and vector: recombinant DNA-derived proteins (e.g. hepatitis B); inactivated viruses (e.g. polio); virus-derived subunits (e.g. influenza); live attenuated viruses (e.g. measles-mumps-rubella, varicella); vectored antigens; and nucleic acid vaccines (currently under investigation). Generally, OVRR reviews vaccines for infectious diseases while the Office of Therapeutics reviews vaccines against self-antigens (e.g. cancer vaccines). Classical vaccines that could become persistent include varicella, oral polio and measles. In regard to vectored vaccines, pox would not be expected to persist while herpes virus-derived vaccines would be expected to persist. She did not expect Adenovirus vaccines to persist, but acknowledged the need for clarification of the basis of that expectation and the definition of "persistence."

Dr. Nabel described the possible risks associated with gene-based vaccines as including genotypic damage and the immunologic consequences of expressing a foreign gene *in vivo*. Risk-benefit needs to be considered in context of the population since vaccines are often administered to healthy individuals. He reviewed the gene transfer literature for vectors also used as vaccines. Persistence would be expected with integrating vectors such as retroviral and AAV. Among the other vectors, such as Ad, he concluded that persistence was not observed if the transgene was exogenous. Dr. Nabel offered the following recommendations: regulatory review should be accomplished through FDA; appropriate public disclosure should take place using the Vaccines and Related Biological Products Advisory Committee (within CBER); exemption should be granted for exogenous genes with transient expression; disclosure should be provided to the RAC for self-genes with no persistent expression; disclosure should be provided to the RAC, and review held, for self-genes with persistent expression; disclosure should be provided to the RAC, and review held, for exogenous genes with persistent expression (e.g. AAV). Alternatively, the FDA review process could deal with this category.

A. RAC Discussion

Dr. Breakefield commented on the difficulty, at the institutional level, of interpreting toxicity questions, especially protocols involving the interface between gene transfer vectors and vaccines. In regard to persistence, she thought vector genome persistence should also be considered because of the potential for recombination or reactivation of the transgene. She also noted that therapeutic approaches are limited to sick populations and therefore have a lower risk-benefit ratio, whereas prophylactic vaccines will be used on a larger population of mostly healthy individuals.

Dr. Aguilar-Cordova reminded everyone that the RAC is not a regulatory body but provides a public arena for discussing the transfer of genetic material and the issues relating to such transfer. The RAC provides a certain level of confidence to the public that nothing untoward is happening in the gene transfer field.

Dr. Mickelson said that although she did not know how many vaccine trials involve vectors used in gene transfer trials, information about the vectors and the response of the vaccine recipients—a much larger population than in gene transfer trials—may inform the RAC in its reviews of gene transfer protocols.

Dr. Gordon noted that the wording of the current clause is an attempt to anticipate every situation that might arise in the gene transfer field which is an impossible goal. He stated that the goal should be to replace vagueness with flexibility. He suggested including in the wording a statement about the need for periodic review, by the appropriate FDA and OBA authorities, to assess what should be reviewed by the RAC and what may no longer need RAC review.

Dr. Patterson noted that, of the 35 protocols submitted to the RAC during the past several years using cancer vaccine gene transfer approaches, only one was selected for full RAC public review.

Dr. Markert stated that the word "persistence" should not be used since many of the immunizations will persist, particularly in lymph nodes. She recommended that "integrated vectors that modify the genome"

would be a more appropriate term than "persistence".

Dr. Ando expressed concern about adding additional review for vaccine trials that are already fairly stringently regulated and involve large numbers of research participants.

Dr. Gordon reiterated that, rather than listing specific criteria for triggering RAC review, the wording should include general criteria that could be evaluated by the RAC and FDA to decide on a case-by-case basis which kinds of trials would require RAC review. He suggested the following criteria: duration of expression, timespan during which the genetic material is retained, integration of the material, and other potential pathological effects of the vector such as germ-line insertion. These issues would not automatically trigger RAC review, but they would automatically be reviewed by some (to-be-created) body that would decide whether RAC review was necessary.

Dr. Nabel suggested that a Points to Consider document lay out the criteria for required RAC review. He cautioned against using a blanket exclusion for any class of vectors. Whatever document is crafted, Dr. Nabel advocated that it take into account the necessity for making judgment calls on a case-by-case basis.

Dr. Mickelson asked Dr. Midthun how many protocols that fall within the category being discussed have been submitted to FDA. Dr. Mithun responded that few have.

Dr. Aguilar-Cordova expressed concern about inconsistencies that may not be understandable to local review boards, investigators, and the public. The RAC reviews protocols that involve only a few research participants; to say that a protocol involving thousands of research participants may not need such public review appears inconsistent, at least on its face. The gene transfer database would be incomplete without the vaccine events.

Dr. DeLuca pointed out the vagueness of the current guidelines. A member of the RAC would think that a vector encoding an immunogen used in an infected individual would be therapeutic and, therefore, be subject to RAC review, whereas FDA interprets that protocol as a vaccine trial that would not be subject to RAC review.

Dr. Midthun added the importance of keeping in mind the need to facilitate vaccine development, especially in the human immunodeficiency virus (HIV) arena. Whatever mechanism or definition is developed should not impede the development of these important and needed vaccines.

Dr. Patterson summarized the following points:

- In trying to clarify which types of protocols deserve public review and RAC discussion, it will be important to acknowledge and take into account other existing forms of oversight, review, and regulation for these protocols through FDA, the Centers for Disease Control and Protection (CDC), the World Health Organization, and secretarial advisory committees.

- A rational set of criteria are needed to guide and implement the RAC's decision making as well as help from local committees; investigators and sponsors particularly will expect that some degree of scientific rigor and logic be a part of these decisions.

- Fixed criteria may not be appropriate, but specific goals may be able to be stated succinctly and effectively. A working group could begin to articulate some points to consider and could come up with options for mechanisms to deal with this exemption.

B. Public Comment

Ms. Christensen, Targeted Genetics, noted that the process of vaccine trial review is slower than gene transfer trial review, in part because of a number of unknowns. She suggested that a RAC representative attend the VRBP Advisory Committee meetings to gain a better understanding of the issues that might come before the RAC at a later date. Ms. Christensen's primary concern centered on the delay that might be caused by waiting for full RAC review after spending several years working closely with the FDA to

develop a proposed clinical trial.

Ms. Fleming repeated that investigators who work with vaccines based on adenoviral vectors examine the cell line being used to grow the vector, and from that cell line, determine whether there are few or no replication-competent vectors, and assume that, therefore, those vectors would not persist.

C. RAC Decision To Form Working Group

The RAC agreed that a working group should be formed. The following individuals volunteered for the working group: Dr. Aguilar-Cordova, Dr. Ando, Dr. Breakefield, and Ms. Levi-Pearl with Dr. Midthun, Dr. Simek, and Dr. Nabel who are ad hocs. The working group will draft a Points to Consider document as well as propose a more efficient method for information and data exchange between the NIH and the FDA on this issue.

XVI. Revisiting the Scope of the *NIH Guidelines*: Plan of Action/Drs. Juengst and Mickelson

Dr. Juengst summarized the issue of whether the scope of the RAC should be redefined to include genetic modification by methods other than recombinant DNA transfer, such as oligotherapy, artificial chromosomes and organelle transplants, which was first discussed at the September 1999 RAC meeting. The question resurfaces because of the recent report of the first case of human germline genetic modification resulting from the transfer of mitochondrial DNA during ooplasmic transplantation. This work is not currently subject to the *NIH Guidelines*. A gene transfer policy conference (GTPC) was proposed to identify new technologies and to consider modification of the *NIH Guidelines* to bring them under RAC purview.

A. RAC Discussion

In response to Dr. Macklin's request, Dr. Patterson explained that the FDA and CDC have oversight for some issues but currently assisted reproductive technologies are fairly unregulated. She urged that anything proposed by NIH or the RAC be integrated with or at least cognizant of other discussions underway on this issue.

B. RAC Decision To Form Working Group

A working group was formed to consider emerging techologies and to develop recommendations on the scope issues to decide whether there are a significant number of emerging strategies and to report back to the RAC. The working group will consider whether a GTPC should be organized on this issue. Volunteers for the working group were Dr. Juengst (as chair), Dr. Gordon, Ms. King, Ms. Levi-Pearl, Dr. Mickelson, and Dr. Noguchi. The working group will report back to the RAC at a future meeting.

XVII. Data Management Report/Dr. Greenblatt

Dr. Greenblatt reported that a total of 464 Gene transfer research (GTR) protocols have been or are in the process of completing the RAC review process, 14 new protocols were submitted to OBA since the last reporting period, 10 of which were exempted from public review, and 4 of which were selected for public review at this meeting. Of the 464 protocols, 38 were for gene marking, 424 were for gene transfer, and 2 were nontherapeutic in normal volunteers. A breakdown of the 424 GTR protocols indicates that:

- 290 were for cancer.
- 51 were for monogenic diseases (cystic fibrosis and hemophilia were the most numerous).
- 35 were for infectious diseases (predominantly for HIV).
- 48 were for other diseases (coronary artery disease and peripheral artery disease were the most numerous).

A. Amendments and Updates and Adverse Events

In the past reporting period, 83 amendments and updates were submitted to OBA, all of which were minor, including new clinical sites, additional investigators, annual updates, status changes, IRB/IBC approvals, revised informed consent documents, and responses to recommendations from the RAC. Ten responses to Appendix M-I-C-1 were also received.

Analysis of SAE reporting for this period indicated that, of the 202 serious or unexpected reports submitted to OBA, 68 percent were initial reports and 32 percent were follow-ups. None of the 19 percent of the reports classified as serious, possibly associated, and unexpected required discussion.

XVIII. Discussion of Human Gene Transfer Protocol #0104-467: VEGF Gene Transfer for Diabetic Neuropathy

Principal Investigator:	Jeffery M. Isner, M.D., Tufts University School of Medicine and St. Elizabeth's Medical Center
RAC Reviewers:	Drs. Ando and Juengst
Ad hoc Reviewers:	David J. Fink, M.D., University of Pittsburgh Robert D. Simari, M.D., Mayo Clinic

A. Protocol Summary

Among diabetics, peripheral neuropathy is common and ultimately accounts for significant morbidity. A common consequence of such sensory deficits involving the lower extremities is foot ulceration initiated by trauma that is not apparent to the patient. Such ulcerations often lead to lower extremity amputation, a complication that occurs 15 times more often among diabetic than non-diabetic patients.

Preliminary clinical studies have demonstrated improvement in the signs and symptoms of sensory neuropathy in research participants with lower extremity vascular occlusive disease following intramuscular (IM) injection of naked DNA encoding vascular endothelial growth factor (VEGF). To determine whether such a strategy could be applied to diabetic patients, including those without evidence of large-vessel occlusive disease, the researchers investigated the hypothesis that experimental diabetic neuropathy results from destruction of the vasa nervorum and can be reversed by administration of an angiogenic growth factor. In two different nonhuman animal models of diabetics, nerve blood flow and the number of vasa nervorum were found to be markedly attenuated, resulting in severe peripheral neuropathy. In contrast, following VEGF gene transfer, vascularity and blood flow in the nerves of treated nonhuman animals were similar to those of nondiabetic controls. Constitutive overexpression of VEGF resulted in restoration of large- and small-fiber peripheral nerve function. These findings implicate microvascular disruption as the basis for diabetic neuropathy and suggest that angiogenic growth factors may constitute a novel treatment strategy for this disorder.

The investigators of this proposed clinical trial seek to address the following two objectives: (1) to evaluate the safety and impact of phVEGF165 gene transfer on sensory neuropathy in research participants with diabetes and associated macrovascular disease involving the lower extremities and (2) to evaluate the safety and impact of phVEGF165 gene transfer on sensory neuropathy in research participants with diabetes without macrovascular disease involving the lower extremities.

The protocol is designed as a Phase I/II, single-site, dose-escalation, double-blind, placebo-controlled study to evaluate the safety and impact of phVEGF165 gene transfer on sensory neuropathy. Diabetic males or females older than 21 years of age with sensory neuropathy, with or without macrovascular disease, will be eligible. A total of 192 research participants will be recruited into two arms of the study (each arm consisting of 96 research participants) over 4 years, with the fifth year limited to followup examinations. The 96 participants in each of the two arms of the study will be placed into three cohorts, each consisting of 32 participants. Within each of these cohorts, participants will be randomized to receive phVEGF165 or placebo based on a 3:1 randomization ratio; at the completion of the study, each of 24 research participants will have received a per-treatment dose of 1, 2, or 4 mg of phVEGF165, and 24 participants will have received placebo. Doses will be employed in a serial dose-escalation fashion.

The entire volume of the study drug will be divided and delivered in eight IM injections administered into the foot, calf muscle, or distal thigh muscle of the affected extremity. Following the initial set of injections, repeat treatment with an identical dose will be provided 2 and 4 weeks after the initial dose.

B. Written Comments From Preliminary Review

This protocol was selected for public review by three RAC members. Drs. Ando and Juengst submitted written reviews, as did *ad hoc* reviewers Drs. Fink and Simari, to which the investigators responded in writing and during the meeting.

Dr. Ando noted that this protocol represents a positive example of an academic investigator translating a finding in nonhuman animals into a potential treatment for humans. He requested discussion from Dr. Isner (the PI) about how he obtained funding and how he was able to get all of the various reporting systems in place. Dr. Ando's concerns included whether any rat data were available regarding long-term diabetic retinopathy and biodistribution of the vector to the retina, and the pharmacologic assessments of the VEGF secretion suggesting higher levels in tissues near the site of injection. He also requested a comparison of the use of recombinant protein to DNA gene transfer.

Dr. Juengst's major concern centered on the placebo-control arm of the study and, indirectly, the large number of research participants required. He approved of two specific arrangements: contracting with an independent external data monitor to oversee the clinical practices and data gathering during the course of the study, in supplement to the work of the study's internal DSMB, and making arrangements with St. Elizabeth's Medical Center to assume the medical costs of research-related injuries to research participants.

Dr. Fink's primary concerns related to dosing every 2 weeks, definition of the research participant population (how sensory neuropathy will be determined and whether the individuals have type 1 or type 2 diabetes), and using appropriate outcome measures to assess sensory neuropathy improvement. He commented that the background data (i.e., preclinical information and ancillary information from clinical studies) are impressive and supported using VEGF to treat diabetic neuropathy. Lacking an appropriate nonhuman animal model, human studies are required and in this situation, a standard practice in pharmocology. Dr. Fink suggested that this trial should be separated into two trials: one addressing VEGF-treated diabetic sensory neuropathy and one addressing neuropathy with macrovascular disease.

Dr. Simari presented a review of previous studies and the concerns associated with this type of research. His safety concerns included unintended angiogenesis from exposure to local or systemic VEGF. Due to the diabetic population proposed, he had increased concerns about the risk of edema, which is less tolerable in diabetics. The risk of proliferative retinopathy should be considered for research participants without macrovascular disease since there has been no demonstrated benefit in that population. In regard to the study design, concerns included the large number of research participants (192) and the dosing schedule of 3 injections every 2 weeks (other researchers have injected every 4 weeks).

C. RAC Discussion

Dr. Gordon suggested that the investigators conduct commonly recommended, age-appropriate cancer screening of the research participants prior to enrollment/treatment. He expressed concern about how the investigators would inject the genes into muscle, including how much area must receive VEGF to induce physiologically significant neovascularization, how VEGF spreads, and how extensively it spreads.

Ms. King reiterated Dr. Fink's question about enrolling diabetic research participants who have macrovascular disease if the focus of the trial is on figuring out whether this gene transfer regimen addresses sensory neuropathy.

D. Investigator Response

Dr. Isner described his funding sources. He applied to NIH for a Center of Excellence in Gene Therapy project grant and is waiting for results. This grant would assume much of the cost involved with the regulatory aspects of this protocol. In case that grant is not funded, Dr. Isner also sought philanthropic

support a year ago and identified an individual who made a generous contribution to St. Elizabeth's Medical Center to establish a center for gene therapy that would provide some of the funding required for external monitoring. In addition, the medical center has contributed by setting up a plasmid vector laboratory.

In response to Dr. Juengst's questions, Dr. Isner explained that the overwhelming sentiment of the scientific and regulatory communities has been in favor of including controls in Phase I trials; in addition, FDA specifically recommended that controls be used in this trial. The design of this protocol is in large part a response to the criticism received in the past for not including such controls.

Regarding the number of research participants enrolled, Dr. Isner pointed out that this trial is a dose-escalation trial that will examine several safety issues across different doses. The safety and efficacy data could be extracted from this trial, and then a Phase III trial could be powered adequately with a larger number of research participants to establish a conclusive result.

Dr. Isner also responded to questions about VEGF levels. Information in the literature is contradictory, with some trials of viral vectors reporting no circulating levels of VEGF in plasma or serum and others reporting circulating VEGF levels. He reported that his research has shown an increase in circulating VEGF levels, with IM injection in the leg or intramyocardial injection in the heart, that peaks at about 12 days after gene transfer and has been in the picogram-per-milliliter range (considered a low-level result).

After consultation with Dr. Karl Csaky, Laboratory of Immunology, National Eye Institute, Dr. Isner reported that to date there is no evidence that circulating VEGF protein can cross the blood-ocular barrier; thus, even in the presence of a small amount of VEGF circulating for a brief period, ocular pathology is unlikely. This trial will be conduct a serial ophthalmologic examination. All results will be submitted routinely and systematically to the DSMB that is chaired by the head of the ophthalmology department at Tufts University School of Medicine. According to ophthalmologists consulted, an unexpected ocular outcome could be treated successfully with laser therapy, which is similar to the treatment for any spontaneous episode of retinopathy.

Regarding Dr. Simari's concern about edema, Dr. Isner responded that edema has developed in about one-third of the research participants treated, and it has responded well to oral outpatient diuretic therapy, resolving within 7 to 10 days without any obvious sequelae.

Dr. Isner responded to the concern about dosing every 2 weeks rather than the more usual every 4 weeks. The rationale for this strategy is based on the findings that research participants receiving direct IM injection of naked DNA, VEGF gene transfer typically show robust but inconsistent expression at 1, 2, and 3 weeks, and by 4 weeks, no expression is seen in nonhuman animal models. Dosing every 2 weeks narrows the interval to produce more consistent expression, although Dr. Isner acknowledged that it is unknown whether this regimen will lead to a higher likelihood of adverse side effects.

Regarding Dr. Fink's question about motor velocity vs. sensory measurements, Dr. Isner explained that he consulted Dr. Alan Roper, who wrote the classic text on peripheral neuropathy. Dr. Isner learned that calculation of motor amplitude and velocity is a more robust measurement than sensory measurements.

Dr. Isner answered Dr. Fink's and Ms. King's questions about enrolling diabetic research participants who have macrovascular disease by stating that the study design was intended to address the potential efficacy of the experimental approach in both populations—those with and those without macrovascular disease. The investigators wanted to study a group with macrovascular disease because of results from an initial 23-patient cohort that hinted at efficacy in this group.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Mickelson summarized the following RAC recommendations:

- In the inclusion criteria, more detail is needed regarding the measurement of the extent of sensory deficit.
- Discussion of outcome measures should be added to the protocol.
- There appears to be no reason to break up this trial into two studies.
- Standard precancer screenings should be included in the pre-protocol battery of tests.

It was noted that all other points had been answered by the investigators, including the shift in time of administration. Drs. Ando and Juengst requested that the letter to the investigators include positive feedback about the proposed conduct of the trial.

G. Vote of the Committee

The vote on these recommendations was 10 in favor, 0 opposed, and 0 abstentions.

XIX. Chair's Closing Remarks/Dr. Mickelson

Dr. Mickelson noted that the next RAC meeting is scheduled for September 5-7, 2001.

XX. Adjournment/Dr. Mickelson

Dr. Mickelson adjourned the meeting at 2:35 p.m. on June 15, 2001.

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

Amy P. Patterson, M.D.
Executive Secretary

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

Date:

Claudia A. Mickelson, Ph.D.
Chair

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Attachment II
Attendees

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Andrew Byrnes, FDA
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Massimo Cardinali, FDA
Jeffrey W. Carey, GenVec
Barrie J. Carter, Targeted Genetics Corporation
Janice Castillo, Avigen
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Janice Chappell, DirectGene
Philippa Charlton, ClinTrials Research
Janet Rose Christensen, Targeted Genetics Corporation
Shirley M. Clift, Cell Genesys
Carlos Crohare, National Narrowcast
Aimee Curtwright, American Association for the Advancement of Science
Karen H. Darcy, Genetic Therapy
Joann C. Delenick, citizen
Cynthia M. Dunn, University of Rochester Medical Center
Matthew J. During, Jefferson Medical College
Darian D. Dwyer, Caption Reporters
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Jim Foss, Stellar Systems
Joyce Frieden, BioMed Net
Larry Glaser, citizen
Chad Gorski, Hearings-On-The-Line
Elliott Grossbard, Avigen
Lauren Hafner, *FDC Reports*
Michael J. Hawkins, Washington Hospital Center
Atm Hoque, FDA
J. Denise Hovermale, DirectGene
Beth Hutchins, Canji
Jeffrey M. Isner, Tufts University School of Medicine and St. Elizabeth's Medical Center
Dorothy Jessop, citizen
Michael Kaplitt, New York Hospital and Weill Medical College, Cornell University
Arifa Khan, FDA
April Kimble, Capital Women's Care
Ivan King, Vion Pharmaceuticals
Steven A. Kradjian, Vical
LaVonne Lang, Pfizer
Brian J. Ledwith, Merck & Co.
King Lee, Vion Pharmaceuticals
Lucia Lee, FDA
Mary Levins, Levins Associates
Andrew Lewis, FDA
Dorothy J. Margolskee, Merck & Co.
Nancy S. Markovitz, FDA
J. Tyler Martin, Sr., Valentis
Robert W. Martin, Genzyme Corporation
Valerie McDonnell, Althea Technologies
Maritza McIntrye, FDA
Paul A. Meyers, Memorial Sloan-Kettering Cancer Center
Andra E. Miller, The Biologics Consulting Group

Samuel I. Miller, University of Washington School of Medicine
Sandra L. Morseth, Milestone Biomedical Associates
Manal A. Morsy, Merck & Co.
Tina Moulton, FDA
Bentley J. Moyer, Valentis
John J. Nemunaitis, U.S. Oncology
Jeffrey M. Ostrove, Ceregene
Keith Peden, FDA
Phil Pendergast, Ohio State University
Douglas Pratt, FDA
Andrew Quon, Association of American Medical Colleges
Sumit Raniga, Jefferson Medical College
Darren Rountree, Caption Reporters
Rachel Salzman, Foundation to Stop ALD
Lee Pai Scherf, FDA
Jay J. Siegel, FDA
Janet Skidmore, Merck & Co.
Stephen C. Stickells, Millennia Partners
Mario Sznol, Vion Pharmaceuticals, Inc.
Daniel M. Takefman, FDA
Scott Thaler, Merck & Co.
Dianna Thomsen, King & Spalding
Ori Twersky, Reuters
Dale VanderPutten, DirectGene

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
AE	adverse event
BSL	biosafety level
CBER	Center for Biologics Evaluation and Research, FDA
CD	cytosine deaminase
CDC	Centers for Disease Control and Prevention
COI	conflict of interest
DBS	deep brain stimulation
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
E. coli	*Escherichia coli* bacterium
FDA	U.S. Food and Drug Administration
5-FC	5-fluorocytosine
5-FU	5-fluorouracil
FOIA	Freedom of Information Act
GABA	gamma-aminobutyric acid
GAD	glutamatic acid decarboxylase
GCP	good clinical practices
Gpi	golbus pallidus
GTPC	Gene Transfer Policy Conference
GTR	gene transfer research
HIV	human immunodeficiency virus
IBC	Institutional Biosafety Committee
IM	intramuscular
IND	investigational new drug
IRB	Institutional Review Board
IV	intravenous
LPS	lipopolysaccharide
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
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*
OBA	Office of Biotechnology Activities
OC	osteocalcin
OD	Office of the Director (NIH)
OER	Office of Extramural Research
OVRR	Office of Vaccine Research and Review, FDA
PCR	polymerase chain reaction
PD	Parkinson's disease
PHS	Public Health Service
PI	principal investigator
RAC	Recombinant DNA Advisory Committee
RG	risk group
STN	subthalamic nucleus
UNC	University of North Carolina
VEGF	vascular endothelial growth factor
VRBP	Vaccines and Related Biological Products (Advisory Committee, CBER)