RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

September 20, 2006

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

Contents

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
Minutes of Meeting[1]

September 20, 2006

The Recombinant DNA Advisory Committee (RAC) was convened for its 105th meeting at 12:00 noon on September 20, 2006, at the National Institutes of Health (NIH), Natcher Building, Conference Room D, Bethesda, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 12:00 noon until 5:10 p.m. on September 20. The following individuals were present for all or part of the meeting.

Committee Members

Stephen Dewhurst, University of Rochester Medical Center
Howard J. Federoff, University of Rochester
Ellen E. Grant, HealthNow New York Inc.
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation
Steven Piantadosi, Sidney Kimmel Cancer Center
Michael R. Rosen, Columbia University
Naomi Rosenberg, Tufts University
Robyn S. Shapiro, Medical College of Wisconsin
Nikunj V. Somia, University of Minnesota, Twin Cities
Scott E. Strome, University of Maryland Medical Center
Richard G. Vile, Mayo Clinic College of Medicine
David J. Weber, The University of North Carolina at Chapel Hill

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

Amy P. Patterson, Office of the Director (OD), NIH

***Ad Hoc* Reviewers and Speakers**

Don M. Gash, University of Kentucky
Lee-Jen Wei, Harvard University

Nonvoting Agency Representatives

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

NIH Staff Members
Kelly Fennington, OD
Linda Gargiulo, OD
Mary Groesch, OD
Bob Jambou, OD
Laurie Lewallen, OD
Maureen Montgomery, OD
Marina O'Reilly, OD

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

Amos Panet, National Institute of Allergy and Infectious Diseases, NIH
Gene Rosenthal, OD
Thomas Shih, OD

Others

There were 37 attendees at this 1-day RAC meeting.

Attachments

Attachment I contains lists of RAC members, *ad hoc* reviewers and speakers, and nonvoting agency and liaison representatives. Attachment II contains a list of public attendees. Attachment III is a list of abbreviations and acronyms used in these Minutes.

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

Dr. Federoff, RAC Chair, called the meeting to order at 12:00 noon on September 20, 2006. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on September 7, 2006 (71 FR 52808). Issues discussed by the RAC at this meeting included public review and discussion of one protocol, a gene transfer safety assessment board report, and a presentation and discussion regarding biosafety considerations for research involving lentiviral vectors.

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

II. Roundtable Introduction of RAC Members/Dr. Federoff

Because of the presence of many new RAC members at this meeting, Dr. Federoff asked each RAC member, whether a continuing or new member, to provide introductory remarks that included name, institution, and training and experience relevant to the RAC.

III. Discussion of Human Gene Transfer Protocol #0607-788: Multicenter, Randomized, Double-Blind, Sham Surgery-Controlled Study of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV-2]-Neurturin [NTN]) to Assess the Efficacy and Safety of Bilateral Intraputamenal (IPu) Delivery in Subjects with Idiopathic Parkinson's Disease

Principal Investigator:	William J. Marks, Jr., M.D., University of California, San Francisco
Submitter:	Raymond T. Bartus, Ph.D., Ceregene, Inc.
Additional Presenters:	C. Warren Olanow, M.D., Mount Sinai School of Medicine, and Jeffrey M. Ostrove, Ph.D., Ceregene, Inc.
Presenters by Phone:	Kerry Hafner, Ph.D., PRA International, and Paul Larson, M.D., University of California, San Francisco
RAC Reviewers:	Drs. Dewhurst and Federoff, Ms. Shapiro, and Dr. Somia
Ad hoc Reviewers:	Don M. Gash, Ph.D., University of Kentucky, and Lee-Jen Wei, Ph.D., Harvard University

Drs. Albelda, Ertl, Heslop, Muzyczka, and Nemerow recused themselves from review of this protocol due to conflicts of interest.

A. Protocol Summary

Parkinson's disease (PD) is a gradually debilitating neurodegenerative disorder that currently afflicts approximately more than 1 million people in North America. Characteristic features of PD include trembling of hands, arms, and legs; stiffness of limbs and trunk; slowness of movement; and impaired balance and coordination. These movement-related symptoms correspond with the progressive loss of function, degeneration, and death of neurons in the substantia nigra (SN). SN neurons normally coordinate muscle movement by releasing a signaling chemical called dopamine into other regions of the brain, notably the caudate and putamen. However, as SN neurons degenerate and die in PD, dopamine is lost and the disease worsens.

The dopamine precursor, levodopa (L-Dopa), is the standard of care therapy for PD and acts by improving dopaminergic function of the degenerating nigrostriatal cells. While L-Dopa offers palliative treatment for symptoms, it does not retard progression of the disease. Moreover, the effectiveness of L-Dopa gradually declines and leads to the emergence of L-Dopa induced uncontrollable movements. Striatal dopamine levels and levels of the dopamine synthesizing enzyme, tyrosine hydoxylase, may be reduced by as much as 80% when parkinsonian symptoms first appear. However, the loss of nigral neurons and nigrostriatal terminals appears to be far less severe, with only a 30-50% reduction at symptomatic onset. The population of nigrostriatal neurons that are structurally intact but have lost phenotypic dopamine expression represents a target for restoration and protection.

Several proteins known as neurotrophic growth factors can augment the function of nigrostriatal dopaminergic neurons and protect them from degeneration. Glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTN) are two of these well-characterized factors. NTN is a naturally occurring functional and structural analog of GDNF. There have been numerous studies conducted which have demonstrated the comparable beneficial effects of GDNF and NTN in animal models of PD. In addition clinical studies have been conducted that have also evaluated the safety of GDNF administered directly into the brain of PD patients.

An adeno-associated virus serotype 2 (AAV2) based vector will be used for targeted delivery of NTN to nigrostriatal neurons. In nonclinical studies, the AAV2-based vector encoding NTN, known as CERE-120, has been shown to effectively deliver the neurotrophic factor to nigrostriatal system and protect nigral dopaminergic neurons form degeneration in both rodent and non-human primate (NHP) models of PD. In addition, extensive rodent and NHP safety/toxicity studies have shown that administration of CERE-120 to the striatum is safe and well-tolerated.

In 2005, a Phase I clinical study was initiated to investigate the safety and tolerability of CERE-120 administration to the nigrostriatal system of 12 subjects with moderate to advanced Parkinson's disease (six subjects for each of two doses tested). To date, no serious adverse events related to the CERE-120 or the surgery have been observed. All subjects exhibited improvement in their total Unified PD Rating Scale (UPDRS) scores as well as their UPDRS motor subscale scores practically defined off condition. An independent Data Safety Monitoring Board (DSMB) reviewed the data monthly over the course of the study, and concluded that the study had met its stated primary endpoint, demonstration of safety and tolerability of CERE-120 for the three-month period post-administration.

The double-blinded sham-controlled Phase 2 trial will examine 51 subjects with PD, randomized at a 2:1 ratio of CERE-120 to sham surgery. A single dose level of CERE-120, $5.7x10^{11}$ vector genomes, which is the higher of the two doses in the Phase I study, will be tested. Sham surgery will consist of partial burr holes into the skull, appearing to the subject and physician equivalent to those used to administer CERE-120, but with no breach of the inner lining of the skull. As a double-blind study, each subject, as well as the physicians performing their assessments, will not know their treatment group.

The primary objective of the trial is to evaluate the efficacy of bilateral intraputaminal CERE-120 administration. Efficacy will be assessed by comparing the change from baseline in UPDRS motor score in the practically defined off condition between CERE-120 and sham surgery at nine months post-administration. Secondary measures will include UPDRS-off at earlier time points, motor assessment

when medication is active (UPDRS-on) at several time points, assessments of behavior and mood, activities of daily living, dyskinesia ratings, individual-reported outcome measures, and participant and physician clinical global impression ratings. Safety also will be monitored through spontaneous AE reports, laboratory test results, neurological and psychological tests, and changes in magnetic resonance imaging. Participants will be monitored for development of antibodies to CERE-120 and/or NTN. Additionally, positron emission tomography (PET) scans will be performed in a subset of the participants, at baseline and at 9 months postadministration, to anatomically evaluate functional effects in the brain. An independent safety monitoring board will review safety data at selected intervals and other time points as necessary during the study. Participants will be evaluated annually for the rest of their lives.

B. Written Reviews by RAC Members

Five RAC members voted for in-depth review and public discussion of the protocol. Key issues included questions about whether sufficient safety and efficacy data have been collected and analyzed from the Phase I study, whether the risks to the control group participants are balanced by potential benefits, and whether the proposed number of participants in the control group is sufficient to demonstrate efficacy.

Dr. Dewhurst requested the full safety and follow-up data for all 12 participants in the Phase I trial, particularly efficacy data or preliminary efficacy information that would inform calculation of the sample size for the proposed Phase II trial. He also asked whether data are available on continued long-term follow-up of NHPs. Dr. Dewhurst asked the investigators to explain and justify the decision to include a sham surgery control group in the proposed Phase II trial and to provide a more detailed sample size calculation that incorporates preliminary information from the Phase I study. He wondered how participants would be selected for the fluorodopa study (N=20) within the larger Phase II trial, and how selection bias would be minimized for that study. Give the small sample size of six and the relatively short follow-up, he asked whether it is prudent for the investigators to assume long-term safety. Regarding the informed consent document, Dr. Dewhurst noted that the term “gene therapy” was used in multiple locations, and he suggested that the document be more cautious with respect to the long-term effects of CERE-120, with particular emphasis on defining “long-term.”

Dr. Federoff also asked for more extensive justification of the inclusion of a sham control group. Given the known risks of deep sedation or general anesthesia and those associated with a partial depth burr hole, skin incision among others, he requested a review of the alternatives to sham surgery. He asked how Ceregene, Inc. will ensure that neurological procedures at all proposed clinical sites will be performed comparably. He asked for in-depth follow-up information on participants in the Phase I trial and which peripheral blood mononuclear cell (PBMC) studies were undertaken for Phase I participants and how those results informed the kind of study the investigators chose for Phase II participants. He also asked why the investigators propose to conduct the fluorodopa studies on only 20 participants, the parameters to be measured in participants who will and will not be part of the extended “treatment” protocol, and about potential rescue plans if any participants receiving CERE-120 require cessation of NTN production

Regarding the research design, Ms. Shapiro requested that the investigators comment on the justification for the sham surgery control group, including the need to evaluate the placebo effect for this participant population, the risk-benefit balance, alternative research designs that would pose lower risks of harm, and whether there should be a no-treatment arm. She asked the investigators to comment on whether the small sample of participants (six) in the Phase I trial that received the higher dose of CERE-120, combined with the short observation period (4 to 8 months), is sufficient to evaluate long-term safety and to balance benefits compared to risks. Regarding the informed consent document, Ms. Shapiro noted that the document uses the term “gene therapy,” requested clarification about issues such as the control group participants’ enrollment in an open-label followup study of CERE-120, and noted that the statement of no “long lasting CERE-120-related adverse events” might be misleading in light of the short duration of the observation period from the Phase I trial.

Noting that placebo effects should not be a confounding factor in animal studies, Dr. Somia asked the investigators to provide more details about the safety and efficacy they observed in NHP and rodent models of PD using AAV and NTN. He wondered whether the informed consent document should note

the fact that participants might be asked to stop medication to allow for testing, since the testing will be performed "12 hours after medication" and levodopa dosing can range from two to four times daily. Dr. Somia asked the investigators' to state their rationale for using only a subset of participants for the PET scanning and for including the sham surgery as the control arm of this Phase II trial. He also asked about the statistical power of the claim of no toxicity from the Phase I trials, noting that the participants in the higher dose group have been observed for the shortest duration.

Dr. Gash requested clarification of the statistical basis for the experimental design of this Phase II trial, a listing of AEs experienced by the 12 Phase I participants, current data on efficacy, why PET scans are planned for only a subgroup of participants, and what criteria would be used to change the standard PD medications of study participants once the Phase II trial begins. He asked whether two prescreening visits would provide sufficient baseline data for a disease like PD, which is so variable, and suggested that the investigators increase the number of baseline visits and measurements to decrease the "noise" in this study. Noting that a primary concern with CERE-120 dosing is that the expression of NTN cannot be controlled and that side effects might emerge months to years after dosing, Dr. Gash asked the investigators to elaborate on their plans to manage adverse effects that might result from AAV-NTN dosing.

Dr. Wei suggested that the sham surgery be performed only if is "not dramatic"; if it is dramatic, he suggested that patient evaluations be conducted by a third blinded party, without the use of sham surgery. Dr. Wei noted several concerns about whether the planned sample size would be adequate for making helpful inferences. He suggested considering an adaptive design and that the DSMB should perform an interim analysis after 25 participants have reached month 6 or month 9 to determine whether the planned sample size is adequate. In addition to several specific statistical suggestions, Dr. Wei suggested that the investigators keep track of the reasons for missing data so that proper imputations can be performed at the end of the Phase II trial period.

C. RAC Discussion

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

- Dr. Federoff asked whether participants in the Phase I trial were able to reduce their PD medications. Dr. Gash asked whether any significant changes in medication were required as a result of the experimental regimen in the Phase I trial.

- Dr. Gash questioned whether participants in the Phase I trial had experienced any significant weight changes.

- Because accurate tools to quantitate dyskinesia are not available, Dr. Dewhurst asked whether the investigators plan to develop such tools and integrate them into the protocol.

- Dr. Kirchhoff asked about the postoperative infection rate for central nervous system (CNS) injection-type surgeries such as the one proposed for this Phase II study.

- Dr. Vile asked whether there are long-term immunological consequences of overexpressing a self-protein and whether the investigators had encountered antibodies to the product as well as the vector.

- Dr. Federoff asked for clarification of the standards for participant followup.

- Noting that dosing five or six participants per month is a reasonably cautious rate of enrollment, Dr. Dewhurst requested that the investigators formalize that recruitment rate to avoid the possibility of too many participants at once, thereby allowing time to evaluate each dosing group. Dr. Piantadosi added that, depending on how the investigators report their full Phase I findings of

efficacy, potential participants may flock to the Phase II trial and, therefore, some formal rate of enrollment should be established.

- Dr. Piantadosi requested that the investigators give additional serious consideration to unmasking the monitoring committee.

- Dr. Kirchhoff expressed concern about the long list of exclusion criteria. To the extent that the exclusion system is stringent, it creates a numerically small subgroup in the larger group of PD patients. The risk is that that subgroup may not be representative of the general PD patient population, and the long-term risk, if this approach is successful, is that the positive findings will be applied to the larger group.

- To help determine the risks for the sham surgery participants, Dr. Strome asked what type of general anesthesia or sedation would be used during surgery.

D. Investigator Response

In the NHP studies, MPTP-lesioned monkeys were administered CERE-120 or a control agent, and after ten months, significant anatomical and functional effects on the nigrostriatal system were observed. Improved motor function scores, nigral neuron protection, and enhanced tyrosine hydroxylase staining of the striatum and nigra and increased nigral neuron size were observed. In monkeys followed for 12 months, no adverse effects of CERE-120 were observed in the panel of safety/toxicity measures examined.

In the phase I trial, no serious adverse events have occurred to date. Procedure-related adverse events have been mild to moderate in severity, and other adverse events that have been attributed to the product have been those anticipated with increased dopaminergic transmission. No evidence of vector shedding was detected by Q-PCR in serum or urine. No clinically significant anti-NTN serum antibody responses were detected. At the higher dose, two of six subjects demonstrated mild increases in anti-AAV responses. Regarding efficacy data, in the low dose cohort at 12 months, a mean 35% reduction in UPDRS-off scores was observed with evidence of a persistence response in three of three subjects. For the high dose cohort at six months, a nearly 40% reduction in UPDRS-off scores has been observed. Dr. Marks explained that the investigators would be presenting the full efficacy data from the Phase I trial at a professional meeting to be held later in fall 2006. Those data will include the longest level of follow-up, the subscores for rigidity and tremor, analysis of the graded dyskinesia, analysis of the different subsets of motor function, the individual scores, and possibly the PET results if that analysis has been completed.

Regarding the justification for the sham surgery, the investigators cited surgical cases, including several approaches for PD, in which experimental treatments appeared efficacious under open label conditions but proved to be no better than placebo under double-blind sham-surgery conditions. The placebo effect for PD can be substantial but unpredictably variable making alternative study designs difficult to interpret. Ceregene consulted with experts in the field, the independent DSMB, and the FDA regarding the study design. To minimize risk to the sham subjects, partial burr holes are proposed. In a recent review compiling the safety from four different double blind surgical trials for PD, no SAEs were observed in 51 sham subjects. Towards providing some potential for eventual benefit, if upon completion of the blinded portion of the trial CERE-120 is determined to be safe and effective, the sham subjects will gain access to CERE-120 in an open-label extension study.

In response to Dr. Federoff's questions as to how Ceregene, Inc. will ensure that neurological procedures at all proposed clinical sites will be performed comparably, Dr. Bartus noted that the eight sites recruited all have experience in conducting trials involving surgical intervention for PD subjects. Ceregene and the neurosurgeons involved in the Phase I trial would be conducting general training sessions to help assure consistency in target selection and the mechanics of inserting, employing and removing the dosing hardware from the brain.

To avoid bias, the twenty subjects in the fluorodopa study will be selected sequentially in a blinded manner.

No PBMC studies were performed in the Phase I study. The phase II study proposed to archive PBMC samples for possible analysis should AEs occur warranting investigation into cellular immunity.

While there are no medical or surgical approaches to reverse NTN production after gene transfer, the investigators have considered the specific adverse effects associated with other administrations of growth factors for PD and developed strategies for treating each potential symptom. A table of pharmacological treatment strategies was provided.

Regarding Dr. Gash's question about whether two prescreening visits will be sufficient to determine a baseline for a variable disease, Dr. Bartus explained that in the phase I trial the prescreening and baseline scores varied by less that 12%. Given this limited variability and the desire to minimize the hardships to participants caused by multiple visits, the investigators believed two visits to be sufficient.

Changes to PD medications during the trial would be only due to adverse events or lack of efficacy and these criteria would apply to participants in both the study treatment and control arms. Dr. Marks explained that two participants during the course of the trial required a brief reduction in levodopa when they developed dyskinesia. For several days, the investigators reduced their amounts of levodopa, the dyskinesias ceased, and their levodopa medication was returned to the original levels. Dr. Marks explained that the investigators have tried deliberately not to make major medication changes wherever possible so as to be able to determine the effect of the experimental protocol and not introduce confounding factors. However, as research participants reach the point of being 12 months beyond the gene delivery, there may be the possibility of starting to reduce their levodopa levels if it appears that they do not need as much medication.

With regard to longer term development of dyskinesias, Dr. Bartus explained that the investigators have not seen any long-term dyskinesia with the longest participant out to 14 months. All of the several episodes of dyskinesia seen in the Phase I trial were experienced in days to weeks following the experimental procedure and did not recur, despite maintaining all the usual medications at the normal doses. Dr. Bartus acknowledged that the investigators are not certain how to interpret the mild and transient dyskinesias experienced by some of the research participants, even though they describe them as an AE related to the study. The reason these dyskinesias could be related to the treatment may be because merely raising the levodopa dose or dopamine agonist can induce dyskinesias. Because the Phase I protocol called for putting NTN in a targeted area that enhances dopamine activity, it was not unexpected that some of the participants would show enhanced but transient dyskinesia as their system equilibrates to a new level of dopamine activity.

Dr. Marks responded that there seems to be sustained production of the protein, although there are few data points and the longest duration of follow-up is about 14 months. Regarding the possible long-term immunological consequences of overexpressing a self-protein, Dr. Bartus noted that no effects were observed for one year in monkeys and rats at doses that were hundreds of times higher than what produced efficacy.

With regard to antibody against NTN, Dr. Ostrove explained that the investigators used an enzyme-linked immunosorbent assay (ELISA) that was developed in-house; its sensitivity was 30 or 40 nanograms per milliliter. Using that assay, the investigators did not see evidence of antibody against NTN. In addition, the investigators conducted a quantitative polymerase chain reaction analysis looking for vector potentially expressing elsewhere than in the brain, but have seen no evidence of NTN migrating outside of the targeted area, thereby limiting severely its exposure to the immune system.

Since participants have received a gene vector that may allow the protein to be expressed for the individual's lifetime, the investigators will continue following these individuals over the long term. Dr. Bartus explained that the investigators are in the final stages of putting together a long-term followup protocol for all participants that would assess them every 6 months indefinitely. The investigators also

intend to offer participants recruited into the proposed sham treatment group the opportunity for treatment following the break of the blind, and then they also would be followed long term following that treatment.

Dr. Marks noted that there has been no change in mood or cognition for any of the research participants, despite two participants having antecedent diagnoses of depression.

With regard to the tools to measure dyskinesias, Dr. Olanow noted that the investigators have had difficulty developing tools to meet all needs. He explained that the three tools used in this protocol are the UPDRS questions that specifically ask what percentage of the day a PD patient experiences dyskinesia, the motor diary that rates hour by hour, and the abnormal involuntary movement scale in which the individual rates the performance of various activities.

Dr. Marks responded that the investigators are monitoring any significant weight changes and, to date, have noted that weight has been completely stable in these research participants.

In response to the question about the postoperative infection rate for CNS injection-type surgeries, Dr. Larson stated that protocols such as this one are relatively novel and cited two fetal cell transplant studies. Including 34 and 40 research participants, respectively, these studies were conducted with needle passes with injections, and neither study resulted in any infections. Another study that used deep brain stimulation (DBS) surgery, a more mainstream surgical treatment for movement disorders, looked at rates of early infection (likely due to making a skin incision) and late infection (likely related to the implanted hardware). In those 262 patients, the early infection rate within 30 days was 1.5 percent. On the basis of those three studies, Dr. Larson explained that the investigators believe that the likely infection rate for a procedure such as the one they propose, given the timeframe and the small size of the incision, would likely be in the range of 1 percent to 1.5 percent. Dr. Bartus added information from a very small (six participants) Ceregene protocol for delivering nerve growth factor to Alzheimer's disease patients that showed no evidence of infection in any participants in the timeframe of 12 months to 24 months postdosing.

Dr. Olanow expanded on the plans for participant followup. First, the investigators understand that the participants may prefer to be followed longer term by their own health care teams rather than by the protocol team. If that is the case, the investigators will attempt to obtain whatever information is available on each participant, with particular emphasis on any information about AEs. Second, the investigators will offer to see the participants for free forever, creating an incentive for the participants to come back and maintain the relationship. In addition, the investigators plan to send teams out to those participants willing to allow such visits.

With regard to the exclusion criteria, Dr. Olanow explained that the investigators want participants who have advanced PD with motor complications, and the only individuals who would be excluded are those who have conditions that could be mistaken for—but are not—PD. He further explained the exclusion criterion related to participants' scores on the Mini-Mental Status Examination as a further attempt to be reasonably protective of participants: Individuals who have subclinical cognitive impairments who then have eight needle tracks through their brain could be pushed into cognitive defect.

E. Public Comment

Dr. Takefman acknowledged that sham surgeries as controls have been approved by the FDA in the past. In this particular case, the FDA would look at whatever is proposed and evaluate it on its own merits.

Dr. Borror stated that, regulatorily, sham surgery is not prohibited. She reiterated that calculation of the risk-benefit ratio includes not only benefits to the individual participants but also the benefit to society of the knowledge gained.

Dr. Borror suggested that the investigators avoid referring to the intervention as "treatment."

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Scientific/Medical/Study Design Issues

- Protocol #0607-788's focus on a debilitating neurological disease with significant morbidity throughout the world is significant. However, there are number of inherent scientific and ethical challenges to both the study's design and analysis.

- The use of a sham surgery control group is the most important concern, given the risks involved in surgery—partial burr holes and anesthesia. Because no sample size calculation was provided, however, the justification for employing a sham surgery control group is unclear. Moreover, it is not evident that the size of the control group (i.e., 17 participants) will be sufficient to show efficacy of the experimental protocol. The statistical basis of the design, particularly the power calculations used to determine the sample sizes and study duration, should be clarified.

- Because recombinant AAV may infect human neurons and glial cells in a way different from that of nonhuman animal (e.g., rat, monkey) neurons and glial cells, the investigators should not rely on volumetric comparisons to establish the appropriate dose for humans. In other words, the moieties of infection may not translate between species.

- There also may be important differences in the sequence homology between NHP and human NTN, as well as differences in the affinity of the vector for the receptors. These differences in turn may have important effects on the study's safety and efficacy profile.

- The data from the Phase I study should be reexamined to determine the appropriate sample size and duration for the proposed Phase II study.

- The lack of SAEs observed in the Phase I trial (N=12) should not be interpreted to mean that the experimental intervention is without toxicity. Given the small sample size and the potential selection/ascertainment/observer biases and the fact that the proposed dose was determined from a small sample size (i.e., the six participants in the Phase I high-dose arm), statements regarding the safety of the study should be tempered.

- An improved and more detailed methodology for detecting, characterizing, and quantifying AEs (e.g., insomnia, cognitive impairment, affect disorders, dyskinesias, etc.) should be developed and used in the trial.

- Neutralizing antibodies to NTN and glial cell line-derived neurotrophic factor may have clinically significant effects. Given the reported limitations in the sensitivity of the current ELISA assay for anti-NTN antibodies, every effort should be made to procure or develop a more sensitive assay.

- Given the novelty of the study design and the level of intervention involved, it would be prudent to collect participants' PBMCs and store them for future studies when more precise immunologic assays are developed or if questions arise that might be addressed through the analysis of such cells. Consideration also should be given to employing PBMCs to monitor clinical and subclinical immune responses.

- Screening pregnancy tests should be performed within 72 hours of dosing.

- The DSMB should review unblinded data.

- Although the decision to stop a trial will be based on an assessment of risks and benefits, the protocol should provide guidance to the DSMB on the criteria and rules for stopping the study.

- The following additional information should be submitted to the OBA by the investigators:

    - Long-term PET data from the NHP studies

    - Any Phase I data relevant to safety and efficacy that were not presented at the RAC meeting (e.g., ^{18}F- DOPA PET scans, individualized safety and efficacy profiles)

    - The DSMB's charter

    - The protocol being developed for long-term followup of the study participants

Ethical/Legal/Social Issues

- In the consent document:

    - Replace all references to "gene therapy" with "gene transfer" to prevent misunderstanding about the potential benefits of the study. The potential for participants to have a therapeutic misconception is particularly acute in this study because of the severity of the disease.

    - Reword the statement "CERE-120 has been given to 12 people without any long-lasting CERE-120 related adverse effects." The meaning of "long-lasting" is unclear and could convey an inappropriate level of confidence about the safety of the product.

    - Expand the discussion of the risk-benefit ratio for participants receiving sham surgery. Additional information also should be provided about the criteria that will be used to determine which participants in the control group will be eligible to receive CERE-120 at the end of the study.

- The statement on page three regarding the ongoing study, noting "no long-lasting CERE-120 related adverse events," could be misleading in light of the short duration of the observation period and should be revised to acknowledge the limitations of the conclusions to be drawn from the current data.

- Two informed consent documents with and without a discussion of the PET studies should be prepared. The consent without references to the PET studies should be used after the 20 participants for this subcohort have been selected.

G. Committee Motion 1

It was moved by Dr. Weber and seconded by Dr. Vile that the RAC recommendations be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 11 in favor, 0 opposed, 0 abstentions, and 5 recusals (Drs. Albelda, Ertl, Heslop, Muzyczka, and Nemerow).

IV. Minutes of the June 21, 2006, RAC Meeting/Drs. Rosenberg and Vile

Dr. Rosenberg noted that the June 21, 2006, RAC minutes were an accurate representation of the meeting.

A. Committee Motion 2

Although no formal motion was made, the RAC approved the June 21, 2006, RAC meeting minutes by a vote of 9 in favor, 0 opposed, 2 abstentions, and 0 recusals. The abstentions represented RAC members who were not present at the June 21, 2006, RAC meeting.

V. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Albelda, Federoff, and Heslop

Dr. Federoff provided the full report for the period of April 26, 2006, through July 25, 2006.

The OBA received 22 protocol submissions, of which 21 were not selected for public review at this RAC meeting. Of those 21 protocols not selected, 18 were for cancer, two for retinitis pigmentosa, and one for peripheral artery disease; five used adenoviruses, six used plasmids, five used pox viruses, three used retroviruses, one used a herpesvirus, and one used ribonucleic acid transfer.

During the reporting period, the OBA received 95 amendments, of which 35 were site or principal investigator changes, eight were protocol design modifications, and 11 were protocol status changes. There were 14 annual reports, 10 responses to *Appendix M(1)C(1)* of the *NIH Guidelines*, and 17 amendments and notifications.

A total of 165 AEs were reported during this period. Total initial reports numbered 134. Total "A" events reported were 24; 18 initial A events were reported, of which 13 were A1 events and 5 were A2 events. No AEs required public discussion.

VI. Biosafety Considerations for Research Involving Lentiviral Vectors

Presenter: Dr. Dewhurst and Marina O'Reilly, Ph.D., OBA

As a representative of the RAC working group, Dr. Dewhurst presented the RAC guidance document on biosafety considerations for research with lentiviral vectors. Additional members of this working group are Drs. Rosenberg and Somia and LouAnn Burnett, M.S., an *ad hoc* consultant from Vanderbilt University.

The OBA frequently receives questions about the appropriate containment for lentiviral vectors, particularly those derived from human immunodeficiency virus type 1 (HIV-1). Because the *NIH Guidelines* do not explicitly address containment for research with lentiviral vectors, the RAC was asked to provide additional guidance for institutional biosafety committees (IBCs) and investigators on how to conduct a risk assessment of lentiviral vector research.

Dr. Dewhurst summarized the findings and recommendations offered at the March 2006 and June 2006 RAC meetings. He presented the Web page from the OBA Web site (www4.od.nih.gov/oba/rac/guidance/lentivirus_containment/index.htm) and noted that the site includes "Guidance on Biosafety Considerations for Research with Lentiviral Vectors"; Web casts, slides, and minutes from the March 2006, June 2006, and eventually the September 2006 RAC meetings; and the working group members' reviews and recommendations.

The use of lentiviral vectors has been increasing because the vector system has attractive features; however, such research also raises biosafety issues. The basic concern with lentiviral vectors is that they have the theoretical potential to regenerate replication-competent virus as well as the potential for oncogenesis. Those risks may be mitigated by a number of considerations related to the inherent nature of the vector system, the transgene, the titer and amount of vector, and inherent biological containment of animal hosts. For many experiments either biosafety level BL2 or enhanced BL2 containment will be appropriate.

The draft Guidance includes discussion of the risks of lentiviral vectors, general criteria for the risk assessment of these vectors, general containment considerations, discussion of the potential for generation of replication-competent lentivirus (RCL) from HIV-1-based lentiviral vectors, RCL testing, how to deal with nonhuman animal studies, and use of other lentiviral vectors. An important feature of the Guidance is the section on examples of biosafety considerations, which offers three scenarios as general guidance to IBCs.

A. RAC Discussion

Dr. Federoff thanked the working group for preparing this useful document, noting that the sample scenarios lay out a range of possibilities that individual IBCs need to contemplate. The Guidance will be available on the OBA Web site.

VII. Closing Remarks and Adjournment/Dr. Federoff

Dr. Federoff thanked the participants and adjourned the meeting at 5:10 p.m. on September 20, 2006.

[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.
RAC Executive Secretary/OBA Director

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

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

Date: _____

_____
Howard J. Federoff, M.D., Ph.D.
Chair
Recombinant DNA Advisory Committee

Attachment I
Recombinant DNA Advisory Committee Roster

Chair

FEDEROFF, Howard J., M.D., Ph.D.
Senior Associate Dean for Basic Research
Director
Center for Aging and Developmental Biology
School of Medicine and Dentistry
University of Rochester
Room 1-9619
Box 645
601 Elmwood Avenue
Rochester, NY 14642

Members

ALBELDA, Steven M., M.D.
Professor of Medicine
Pulmonary, Allergy, and Critical Care Division
Department of Medicine
University of Pennsylvania Medical Center
Biomedical Research Building II/III
421 Curie Boulevard
Philadelphia, PA 19104

DEWHURST, Stephen, Ph.D.
Professor
Department of Microbiology and Immunology
University of Rochester Medical Center
Box 672
601 Elmwood Avenue
Rochester, NY 14642

ERTL, Hildegund C.J., M.D.
Professor of Pathology and Laboratory Medicine
Leader
Immunology Program
The Wistar Institute
Associate Faculty
School of Medicine
University of Pennsylvania
3601 Spruce Street
Philadelphia, PA 19104

FLINT, Jane, Ph.D.
Professor
Department of Molecular Biology
Princeton University
Lewis Thomas Laboratory, Room 234
Princeton, NJ 08544

GRANT, Ellen E., Ph.D., LSCW-R
Vice President, Behavioral Health, Wellness and Health Promotion
HealthNow New York Inc.
1901 Main Street
P.O. Box 80
Buffalo, NY 14240-0080

HESLOP, Helen, M.D.
Professor of Medicine and Pediatrics
Center for Cell and Gene Therapy
Baylor College of Medicine
MC 3-3320
6621 Fannin Street
Houston, TX 77030

KAHN, Jeffrey P., Ph.D., M.P.H.
Maas Family Chair in Bioethics
Director
Center for Bioethics
University of Minnesota
Boynton Health Service Building, Room N504
410 Church Street, SE
Minneapolis, MN 55455-0346

KIRCHHOFF, Louis V., M.D., M.P.H.
Professor
Department of Internal Medicine (Infectious Diseases) and Epidemiology
University of Iowa
Bowen Science Building, Room 4-403
51 Newton Road
Iowa City, IA 52242

KODISH, Eric D., M.D.
F.J. O'Neill Professor and Chair
Department of Bioethics
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195

MUZYCZKA, Nicholas, Ph.D.
Professor
Department of Molecular Genetics and Microbiology
Director
Powell Gene Therapy Center
College of Medicine
J. Hillis Miller Health Science Center
University of Florida
Room R1-191
1600 Archer Road
P.O. Box 100266
Gainesville, FL 32610-0266

NEMEROW, Glen R., Ph.D.
Professor
Department of Immunology
The Scripps Research Institute
Room R214
10550 North Torrey Pines Road
La Jolla, CA 92037

PIANTADOSI, Steven, M.D., Ph.D.
Director
Division of Biostatistics
Professor of Oncology
Sidney Kimmel Cancer Center
Suite 1103
550 North Broadway
Baltimore, MD 21205

ROSEN, Michael R., M.D.
Gustavus A. Pfeiffer Professor of Pharmacology
Professor of Pediatrics
Department of Pharmacology
Director
Center for Molecular Therapeutics
Columbia University
PH7W-321
630 West 168th Street
New York, NY 10032

ROSENBERG, Naomi, Ph.D.
Professor
Department of Pathology
School of Medicine
Tufts University
Jaharis Building, Room 512
150 Harrison Avenue
Boston, MA 02111

SHAPIRO, Robyn S., J.D.
Professor and Director
Center for the Study of Bioethics
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53266

SOMIA, Nikunj V., Ph.D.
Assistant Professor
Department of Genetics, Cell Biology and Development
Molecular Genetics Institute
University of Minnesota, Twin Cities
Jackson Hall, Room 6-160
321 Church Street, SE
Minneapolis, MN 55455

STROME, Scott E., M.D.
Professor and Chairman
Department of Otorhinolaryngology-Head and Neck Surgery
University of Maryland Medical Center
Suite 500
16 South Eutaw Street
Baltimore, MD 21201

VILE, Richard G., Ph.D.
Consultant
Department of Molecular Medicine
Mayo Clinic College of Medicine
Guggenheim Building, 18th Floor
200 First Street, SW
Rochester, MN 55905

WEBER, David J., M.D., M.P.H.
Professor of Medicine, Pediatrics and Epidemiology
Division of Infectious Diseases
Schools of Medicine and Public Health
The University of North Carolina at Chapel Hill
Burnett-Womack Building, Room 547
Campus Box 7030
Chapel Hill, NC 27599-7030

OBA Director/RAC Executive Secretary

PATTERSON, Amy P., M.D.
Director
Office of Biotechnology Activities
Director
Recombinant DNA Program
Executive Secretary
Recombinant DNA Advisory Committee
Office of Science Policy
Office of the Director
National Institutes of Health
U.S. Department of Health and Human Services
Suite 750
MSC 7985
6705 Rockledge Drive
Bethesda, MD 20892-7985

Ad Hoc Reviewers

GASH, Don M., Ph.D.
Alumni Endowed Chair and Professor
Department of Anatomy and Neurobiology
College of Medicine
University of Kentucky
Magnetic Resonance Imaging and Spectroscopy Center
Davis Mills Building, Room 317
Lexington, KY 40536-0098

WEI, Lee-Jen, Ph.D.
Professor
Department of Biostatistics
School of Public Health
Harvard University
655 Huntington Avenue
Boston, MA 02115

NONVOTING AGENCY REPRESENTATIVES

National Science Foundation

HARRIMAN, Philip, Ph.D.
Program Director
Division of Molecular Biosciences
National Science Foundation
Room 565
4201 Wilson Boulevard
Arlington, VA 22230-1859

U.S. Department of Agriculture

JONES, Daniel D., Ph.D.
National Program Leader/Biotechnology
Cooperative State Research, Education, and Extension Service
U.S. Department of Agriculture
Waterfront Center, Room 3444
800 Ninth Street, SW
Washington, DC 20024

MCCAMMON, Sally L., Ph.D.
Science Advisor
Biotechnology Regulatory Services
Animal and Plant Health Inspection Service
U.S. Department of Agriculture
Unit 98
4700 River Road
Riverdale, MD 20737

U.S. Department of Commerce

LEVIN, Barbara, Ph.D.
Project Leader
Biotechnology Division
National Institute of Standards and Technology
U.S. Department of Commerce
MSC 8311
100 Bureau Drive
Gaithersburg, MD 20899-8311

U.S. Department of Energy

DRELL, Daniel W., Ph.D.
Biologist
Life Sciences Division
Office of Biological and Environmental Research
U.S. Department of Energy
SC-72
19901 Germantown Road
Germantown, MD 20874-1290

U.S. Department of Health and Human Services

Office for Human Research Protections

BORROR, Kristina C., Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
U.S. Department of Health and Human Services
Tower Building, Suite 200
1101 Wootton Parkway
Rockville, MD 20852

U.S. Food and Drug Administration, Office of Cellular, Tissue, and Gene Therapies

TAKEFMAN, Daniel M., Ph.D.
Acting Chief
Gene Therapy Branch
Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
HFM-720
1401 Rockville Pike
Rockville, MD 20852

U.S. Environmental Protection Agency

FREDERICK, Robert, Ph.D.
Program Manager
Office of Research and Development
National Center for Environmental Assessment
U.S. Environmental Protection Agency
MC 8623D
401 M Street, SW
Washington, DC 20460

MILEWSKI, Elizabeth, Ph.D.
Senior Biotechnologist
Office of Prevention, Pesticides, and Toxic Substances
U.S. Environmental Protection Agency
East Tower, Room 625
MC 7201
401 M Street, SW
Washington, DC 20460

LIAISON REPRESENTATIVE

FAYL, Gilbert, Ph.D.
Secretary of External Affairs
European Academy of Sciences and Arts
Brussels, Belgium

Attachment II
Public Attendees

Raymond Bartus, Ceregene, Inc.
Theresa Chan, FDA
Odile Cohen-Haguenauer, Ecole Normale Superieure de Cachan
Jacqueline A. Corrigan-Curay, U.S. Department of Veterans Affairs
Margaret Crowley, Eberlin Reporting Service
William J. Marks, University of California, San Francisco
C. Warren Olanow, Mount Sinai School of Medicine
Jeffrey M. Ostrove, Ceregene, Inc.
Donna R. Savage, Capital Consulting Corporation

Attachment III
Abbreviations and Acronyms

AAV-2	adeno-associated virus serotype 2
AE	adverse event
BSL	biosafety level
CNS	central nervous system
CT	computerized tomography
DBS	deep brain stimulation
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
ELISA	enzyme-linked immunosorbent assay
FDA	U.S. Food and Drug Administration
HIV-1	human immunodeficiency virus type 1
IBC	institutional biosafety committee
MMSE	Mini-Mental Status Examination
MRI	magnetic resonance imaging
NHP	nonhuman primate
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NTN	neurturin
OBA	NIH Office of Biotechnology Activities
OD	Office of the Director, NIH
PBMC	peripheral blood mononuclear cell
PD	Parkinson's disease
PET	positron emission tomography
RAC	Recombinant DNA Advisory Committee
RCL	replication-competent lentivirus
SAE	serious adverse event
SN	substantia nigra
UPDRS	Unified Parkinson's Disease Rating Scale