RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

September 23, 2004

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 23, 2004

The Recombinant DNA Advisory Committee (RAC) was convened for its 97th meeting at 8:30 a.m. on September 23, 2004, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Diane Wara (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 11:50 a.m. on September 23. The following individuals were present for all or part of the meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania Medical Center
W. Emmett Barkley, Howard Hughes Medical Institute
Martha C. Bohn, Northwestern University
Neal A. DeLuca, University of Pittsburgh
David L. DeMets, University of Wisconsin Medical School
Stephen Dewhurst, University of Rochester Medical Center
Thomas D. Gelehrter, University of Michigan Medical School
Helen Heslop, Baylor College of Medicine
Philip R. Johnson, Jr., Columbus Children's Hospital *(via teleconference)*
Terry Kwan, TK Associates
Bernard Lo, University of California, San Francisco
Glen R. Nemerow, The Scripps Research Institute
Madison Powers, Georgetown University
Naomi Rosenberg, Tufts University
Robert D. Simari, Mayo Clinic and Foundation
Richard G. Vile, Mayo Foundation
Diane W. Wara, University of California, San Francisco

RAC Executive Secretary

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

***Ad Hoc* Reviewers/Speakers**

Marc A. Dichter, M.D., Ph.D., University of Pennsylvania *(via teleconference)*
Tiffany Scharschmidt, University of California, San Francisco

Nonvoting/Agency Representatives

Karena Cooper, Office for Human Research Protections
Stephanie L. Simek, U.S. Food and Drug Administration (FDA)

NIH Staff Members

Holly Campbell, OD
Robert Jambou, OD
Laurie Lewallen, 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.

Maureen Montgomery, OD
Marina O'Reilly, OD
Gene Rosenthal, OD
Thomas Shih, OD
Frosso Voulgaropoulou, National Institute of Allergy and Infectious Diseases (NIAID), NIH

Others

There were 39 attendees at this 1-day RAC meeting. Attachment I lists RAC members, *ad hoc* reviewers/speakers, nonvoting/agency liaison representatives, and Office of Biotechnology Activities (OBA) staff members. Attachment II lists public attendees.

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

Dr. Wara, RAC Chair, called the meeting to order at 8:30 a.m. on September 23, 2004. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* was published in the *Federal Register* on August 20, 2004 (69 FR 51689). Issues discussed by the RAC at this meeting included public review and discussion of one protocol, a data management report, and an update on the RAC Gene Transfer Clinical Trial Design Working Group.

Dr. Rose reminded RAC members of the rules of conduct that apply to them as Special Government Employees.

II. Minutes of the June 8-9, 2004, RAC Meeting/Drs. Heslop and Simari

Dr. Heslop thanked the OBA staff for developing complete and well-written minutes of the June meeting. Several non-substantive changes were suggested.

A. Committee Motion 1

Dr. Heslop moved that the RAC approve the June 8-9, 2004, RAC meeting minutes. Ms. Kwan seconded the motion. The vote was 16 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Update on the RAC Gene Transfer Clinical Trial Design Working Group

Presenter: David L. DeMets, University of Wisconsin Medical School
Additional Presenter: Terry Kwan, TK Associates
Additional Presenter: Tiffany Scharschmidt, University of California, San Francisco

Dr. DeMets presented an update on the progress of the RAC Gene Transfer Clinical Trial Design Working Group. The Working Group prepared three written documents and presented each one, including: 1) a draft of basic design guidelines for the gene transfer field; 2) a review of informed consent issues; and 3) a description of design issues in RAC protocols.

The draft guidelines document states that, although there is no single protocol that will work for all diseases and methods of gene transfer, there are basic principles that should be considered in all cases. The following questions should be addressed during the design phase:

- What is the rationale for this protocol?
- What outcomes will be measured?

- What is the population and why?
- What is the basic experimental design and what is the sample size justification?
- What analysis plan and monitoring plan are in place?
- How will the data accumulated be used in designing the next trial or research step?

Dr. DeMets and Ms. Kwan then presented the results of a review of informed consent issues conducted by Mr. Daniel Lipton, an OBA summer intern who was supervised by Dr. Cheryl McDonald, OBA. They reviewed 43 protocols publicly reviewed by the RAC in the past 2 years and examined the consent form descriptions to determine: 1) objectives of the study; 2) research vs. available treatment; 3) gene transfer procedures; 4) dose-escalation explanations; 5) potential benefits; 6) potential risks and discomforts; 7) conditions for trial termination; 8) financial costs of participation; 9) investigator financial conflicts; 10) physician contact information; and 11) procedures for emergencies. The overall conclusion was that approximately 50 percent of the informed consent documents were satisfactory in terms of comprehensibility. The studied protocols were submitted prior to the informed consent guidance posted on the Web, however, the reviewers agreed that additional help is still warranted.

Ms. Scharschmidt, whose internship was supervised by Dr. Lo, prepared the third document, which addresses design issues in gene transfer protocols. She addressed the following questions: How frequently do RAC members raise design concerns in written reviews and public discussions? What are the most common design concerns? How often are design concerns mentioned in the RAC letter to investigators because issues were not resolved in the public discussion? Ms. Scharschmidt examined 43 protocols that were publicly reviewed by the RAC between December 2000 and December 2003. The major concerns identified were selection of subjects, dose escalation, selection of safety endpoints, biologic outcomes, and overall study design. Less frequently raised concerns included data safety monitoring board issues, biostatistical analysis of adverse events or efficacy outcomes. She concluded that study design concerns are commonly raised and usually focus on safety. Her results could provide the basis for a future guidance document or could be the subject of discussion and collaboration involving the RAC, researchers, and others in the gene transfer field.

The next step for the RAC Gene Transfer Clinical Trial Design Working Group will be to integrate these three documents with input from the RAC and working group.

Dr. Rose then asked Dr. DeMets about Phase I trials in gene transfer and whether he's developed an overarching idea about performing these trials more efficiently. Dr. DeMets replied that the whole Phase I design field will need to be evaluated as the gene transfer field advances. He also noted that it will be important to involve colleagues with statistical backgrounds to help develop some of the first principles the field needs to think about. Few biostatisticians are currently involved in such efforts and Dr. DeMets recommended that researchers working in early phase gene transfer seek out biostatisticians for advice and counsel to stimulate new thinking.

IV. Data Management Report/Drs. Heslop, Simari, and Wara

Dr. Simari reported that 20 protocols were submitted since the RAC meeting of June 2004, 1 of which was selected for public discussion. Of the 19 protocols not selected, 13 were for cancer, including 3 non-therapeutic vaccine studies. The types of vectors used included nine plasmid vectors, four adenoviral vectors, two pox vectors, one retroviral vector (lentivirus), one adeno-associated viral vector, and one herpes virus vector. One protocol used RNA transfer.

The OBA tabulated data and provided background information on adverse events (AEs) during the past 3 months; a total of 168 AEs were reported. The data management team reviewed in detail each of the 25 protocols that resulted in AEs classified as "A" events; 12 of those were initial reports. Dr. Simari discussed one of those protocols, #0204-530, "A Randomized Phase II Study of PNF Arrayed Biologic

With 5FU and Radiation Therapy for First-line Treatment of Unresectable Locally Advanced Pancreatic Cancer." The first event occurred when one individual developed pancreatitis 5 days following delivery of the study agent; it was probably related to the administration procedure or the agent. The problem was self-resolved. Two other events occurred shortly thereafter that were also self-resolved: another case of clinical pancreatitis and a case of biliary sepsis and cholangiatis following agent administration that were deemed probably or possibly related to the study agent. Dr. Simari noted that they will continue to closely monitor this protocol.

Dr. Wara reported that 97 protocol amendments and 10 responses to Appendix M had been filed in the past 3 months. Of the 97 amendments, 40 were related to changes in the site or principal investigator.

Dr. Wara then briefly presented issues related to the following five protocols.

A. Protocol #0101-453: A Multi-Center, Open Label, Two Part, Dose Escalation Study to Determine the Tolerability of Interferon-beta Gene Transfer in the Treatment of Recurrent or Progressive Glioblastoma Multiforme.

This open-label, two-part, dose-escalation study was designed to determine the tolerability of interferon-∃ gene transfer in the treatment of recurrent or progressive glioblastoma multiforme. Because of a serious AE related to an inflammatory response in a patient's ventricular region in another protocol, the RAC recommended that participants in Protocol #0101-453 not be accrued if the tumor was adjacent to the ventricle. Following that recommendation, the investigators modified the inclusion/exclusion criteria, and subsequently, the protocol was closed because of the difficulty in accruing study participants.

B. Protocol #0104-468: VEGF Gene Transfer to Promote Angiogenesis in Patients with Advanced Heart Failure.

This protocol involves vascular endothelial growth factor gene transfer to promote angiogenesis in patients with advanced heart failure. The principal investigators requested that the FDA remove the 15-year followup requirement, since the study employs plasmid vectors. They requested instead that active assessments in the post-administration followup period continue for 12 months rather than 15 years.

C. Protocol #0108-494: Gene Transfer of the γc cDNA into CD34+ Hematopoietic Cells of Infants or Children with X-Linked Severe Combined Immune Deficiency (X-SCID).

The study was designed to transfer the γc gene cDNA into CD34+ hematopoietic cells of infants or children with X-linked severe combined immunodeficiency disease (SCID). The submitted proposal requests that the underlying premise for gene transfer as an alternative to haploidentical transplant be medical indication rather than age as enrollment is restricted to infants older than 6 months of age. The protocol was placed on clinical hold following the report of two X-SCID infants with leukemia after gene transfer in France. It is no longer on clinical hold.

D. Protocol #0201-516: Ex Vivo Retroviral Gene Transfer for Treatment of X-Linked Severe Combined Immunodeficiency (XSCID).

This protocol was also placed on clinical hold following the French X-SCID experience and was later released from clinical hold. The protocol involves *ex vivo* retroviral gene transfer of the γc gene for treatment of X-linked SCID. The first participant was enrolled in January 2004, with gene transfer occurring the same month. The child is apparently stable. Gene marking 5 months after gene transfer shows the presence of 0.5 percent marked T cells.

E. Protocol #0307-588: A Phase I Dose Escalation Study of Intra-Articular Administration of tgAAC94, a Recombinant Adeno-Associated Vector Containing the TNFR:Fc Fusion Gene, in Rheumatoid Arthritis.

This protocol was the first injection into joints protocol reviewed by the RAC. It involves intra-articular administration of a recombinant adeno-associated vector (AAV) containing the tumor necrosis factor receptor FC fusion gene in rheumatoid arthritis. It was reviewed during the September 2003 RAC meeting; since that time, two amendments have been received from the investigators. The protocol was initiated in March 2004 and the first participant enrolled on March 16, 2004. Dr. Wara presented this information to indicate how quickly the protocols move forward once they are reviewed by the RAC, as well as the schema in place for the review of amendments and the coordination between the RAC and the FDA.

V. Discussion of Human Gene Transfer Protocol #0407-669: Hippocampal Neuropeptide Y Gene Transfer in Subjects with Intractable Mesial Temporal Lobe Epilepsy

Principal Investigators:	Matthew During, M.D., D.Sc., Cornell University; Itzhak Fried, M.D., Ph.D., University of California, Los Angeles (UCLA); and John Stern, M.D., UCLA
Sponsor:	Neurologix, Inc.
RAC Reviewers:	Drs. Bohn, Dewhurst, Johnson *(via teleconference)*, and Powers
Ad hoc Reviewer:	Marc A. Dichter, M.D., Ph.D., University of Pennsylvania *(via teleconference)*

A. Protocol Summary

Temporal lobe epilepsy (TLE) is the most common form of epilepsy, affecting approximately 2.5 million individuals in the United States. Approximately 30 percent of these individuals are resistant to anti-epileptic drugs (AEDs), and for most patients who do respond to AEDs, the drugs eventually fail. About half of the resistant patients have a form of epilepsy called mesial temporal lobe epilepsy, which is the focus of this study. Although the specific cause of most human epilepsies—including TLE—is unknown, the disease is defined by a propensity for seizures resulting from altered physiology of cells within the temporal lobe. Current understanding of the disease centers on a specific region of the temporal lobe called the hippocampus. Some cells in the region of the hippocampus where seizures start are too excitable and can spontaneously become active, recruiting other cells to become active as well. This synchronous activity of cells in the brain results in a seizure. Although the cells' excitability can often be reduced with the drug therapies currently available, many of those with TLE continue to have frequent and disabling seizures. This situation therefore warrants the investigation of additional therapies.

The approach that has shown the most efficacy to date is temporal lobectomy, an operation that removes the affected brain region. In carefully selected people, the surgery can have a 70 percent success rate (as defined by seizure-free status) over 1 to 2 years. In about 20 to 40 percent of patients, however, seizures recur in the ensuing years. There are significant risks associated with removing this part of the brain, including, for the majority of patients, cognitive loss. In addition, many patients are excluded from this procedure because tests suggest that they are heavily dependent on this region of the brain for memory and verbal functions.

The protocol proposes an initial safety study to provide safety and tolerance data to support a phase II study to determine whether gene transfer using an adeno-associated virus (AAV) vector expressing neuropeptide Y (NPY) with less risk than those associated with temporal lobectomy. The vector would be injected into the temporal lobe in an attempt to reduce the excitability of the brain, stopping seizures in a less invasive manner than a temporal lobectomy.

The study is designed so that the gene transfer will piggyback onto a clinically indicated surgery to implant depth electrodes to determine the location where the seizures originate. Once this location has been identified, the investigators will modify the electrodes used for recording, so they can be used to infuse the viral vector. The second aspect of the protocol that lowers the risk threshold is that participants will have already agreed to undergo a temporal lobectomy. The only deviation from standard care will be the postponement of the surgery from the typical 2 to 4 months following intracranial recording to 6 months. The risks associated with the trial include those related to the use of the AAV vector and NPY

transgene, however, there is no additional surgery required to introduce the vector and there is a built-in "rescue" procedure, wherein, the transduced cells are to be removed *en bloc* in a subsequent clinically-indicated and therapeutic lobectomy.

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

In a unanimous vote, 13 RAC members recommended in-depth review and public discussion of the protocol. RAC reviewers Drs. Bohn, Dewhurst, Johnson, and Powers and *ad hoc* reviewer Dr. Dichter submitted written reviews, to which the investigators responded in writing and during this meeting. Key issues included conflict of interest concerns, methods for selecting appropriate candidates for the procedure, whether participants would have the option of canceling the scheduled lobectomy if the gene delivery procedure benefited them, and possible changes in the protocol to add more subjects. Other questions related to the choice of the vector, its method of delivery, and the extent of analysis to be performed on the resected tissue.

Dr. Bohn noted the importance of the investigators' rescue approach for a procedure involving gene delivery to the nervous system. She then raised the following issues: potential conflicts of interest involving Dr. During and the sponsor; statements in the abstracts that could mislead participants, especially those concerning plans for the lobectomies and the method of administration of the vector; the fact that pre-clinical data were obtained using a different vector than the one proposed in the protocol; and concerns about the extent of analysis of the resected tissue. She emphasized the importance of in-depth analysis of the tissue because the investigators may have the opportunity to obtain a snapshot of gene transfer effects in the nervous system.

Dr. Bohn asked whether participants would have the option of canceling the lobectomy if the gene delivery procedure was of benefit to them and if so, would this necessitate a change in the protocol so that more subjects could be added, ensuring a large enough cohort to provide adequate analysis of tissue. She also asked for the criteria for an early lobectomy should deleterious effects occur. She asked for the rationale for a 1-month delay between dose cohorts and a 2-week interval between subjects and whether these intervals were long enough to assess possible deleterious effects.

Regarding vector administration, she requested data concerning the effect of the 48 nt deletion in the chicken β-actin (CBA) promoter on promoter strength, cellular expression, and stability of expression and asked whether the vector had been tested in the non-human primate central nervous system (CNS). She also asked whether hippocampal sclerosis might interfere with vector distribution or whether the vector might be transported to the contralateral hippocampus, where the rescue strategy will not apply. She requested information about whether phosphate-buffered saline (PBS) is the optimal vehicle for vector delivery, how vector particle aggregation in the high doses would be minimized, and how the percentage of packaged particles would be determined in the vector stocks. She asked for the rationale for undertaking only 2 vector doses at a volume 6 times higher and 10 times more concentrated than in the investigators' ongoing Parkinson's disease trial and for the pre-clinical data supporting these doses.

Dr. Dewhurst stated his approval of the rescue procedure and noted that the overall proposal was carefully constructed. He reiterated some issues that had been raised by Dr. Bohn, including conflict of interest concerns and the use of the CBA promoter. In addition, he asked whether pharmacologic agonists of NPY-Y2 receptors exist and would have therapeutic potential. He also asked why the investigators believe that experiments in spontaneously epileptic rats are not necessary before proceeding with a human trial. He requested any follow-up results from the preclinical studies reported in the *Journal of Neuroscience* article. Specifically, he was interested in whether AAV-driven expression of NPY lasts longer than 3 months and whether protection from KA-induced epilepsy was prolonged. He asked whether potential participants with neutralizing AAV antibodies would be excluded from the trial and for more information about the quality control procedures for the assays to detect anti-AAV or anti-NPY antibodies. He also asked about reproducibility of the physical and genomic titer assays and the sensitivity of the assays to detect replication competent AAV. He asked whether the study exclusions should also include immunodeficient individuals and how the Hamilton syringes would be sterilized prior

to use. He also asked why is the vector produced in New Zealand and then shipped to New York for purification. He was also interested in the reasons drug therapies eventually fail.

Dr. Dewhurst had two suggestions concerning the informed consent document. He recommended that the investigators extend the contraception requirement to include males as well as females and suggested replacing the phrase “gene therapy” with “gene transfer.”

Dr. Johnson noted his agreement with the points made by Drs. Bohn and Dewhurst. He asked the rationale for using the chimeric AAV1/2 vector rather than an AAV2 vector. He expressed concern about the potential for lot-to-lot variation during vector manufacture. He urged the investigators not to exclude or include any research participant on the basis of their anti-AAV titers and to use this protocol as an opportunity to study the effects of pre-existing immunity on gene transduction. He stated that there may be an opportunity to do a plot of gene transduction versus antibody titers and emphasized the importance of collecting and analyzing these data.

Dr. Powers noted the same conflict of interest concern that was raised by other reviewers. He suggested that the vector risk be characterized more precisely and that the language in the informed consent document be changed so that participants are not misled about possible therapeutic benefits.

Dr. Dichter noted his favorable impression of the proposal. However, he was concerned about the potential risk of delaying surgery for several months. People with epilepsy sometimes die suddenly for unexplained reasons. Therefore, there’s a small risk of sudden unexpected death that could take place during the months needed for evaluation. He recommended that this possibility be described in the protocol and added to the informed consent form. He raised the issue of how the investigators will determine whether a potential participant is an appropriate candidate. The criteria for selecting candidates for temporal lobectomy after phase II monitoring is not uniform across epilepsy centers, therefore the protocol should indicate the criteria for the selection of study subjects. He also asked for data on the expected number of appropriate candidates at UCLA based on the investigators’ recent experience.

Dr. Dichter, in agreement with Dr. Bohn’s comments, also asked whether participants would have the option of delaying or canceling the lobectomy if the gene delivery procedure benefited them. He recommended additional preclinical animal studies. He noted that the animal experiments reported on to date are in normal rats, not epileptic rats. He suggested that studies in epileptic animal models are important to investigate vector transduction levels, distribution and efficacy. He also asked whether the glial cells transfected by the AAV-NPY and, if so, what will the consequences be. He asked if overexpression of NPY in inhibitory interneurons could downregulate release of GABA or could have other effects. He requested a review of the investigators’ ongoing Parkinson’s disease trial, as the safety issues are relevant to this protocol.

C. RAC Discussion

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

- Dr. Albelda asked whether the frequency of monitoring patients at 1, 3, and 6 months after injection was sufficient. Dr. During clarified that the patients are called approximately every 2 weeks to update the seizure log.

- Dr. Simari asked about the likelihood of a participant remaining seizure free with placebo treatment or in a control group. Dr. During replied that approximately 8 to 25 percent of patients could remain seizure free after 6 months. He noted that epilepsy is not prone to placebo effects, but that this possibility would be explored in an appropriately controlled Phase II study.

- Dr. DeLuca asked about the contributions of the AAV1 and AAV2 components of the chimeric vector to improved transduction. Dr. During stated that AAV2 capsid has restricted tropism in the target part of the brain, however, the chimeric vector was used rather than an AAV1 vector because of the greater ease in purifying the vector stocks. Dr. DeLuca then asked whether there

are adequate biodistribution studies with the chimeric vector. Dr. During replied that there's a significant amount of data, but in different concentrations and with different animals. He acknowledged that the pre-clinical data set on the distribution expression is not complete at this time.

- Dr. DeMets asked that Dr. During quantify what can be learned and what will not be learned from the small number of patients enrolled in the trial. Dr. During stated that because the investigators will have access to the tissue and can perform in-depth analysis, significant information could be obtained with a small number of participants. However, he agreed that it was reasonable to enroll additional subjects.

D. Investigator Response

Dr. During and colleagues responded with the following information:

To address Dr. Bohn's and others' conflict of interest concerns, Dr. During described his relationship with Neurologix, Inc., the sponsor of the trial. Dr. During is a founder of and consultant to Neurologix, Inc. However, he will have no involvement in patient recruitment, clinical care, or data collection. Drs. Fried and Stern have no relationship with Neurologix, Inc. All of this information will be stated in the final version of the informed consent document. In response to a comment by Dr. Dewhurst, Dr. During stated that someone not directly affiliated with the trial would select the independent data monitoring committee and the medical safety monitor.

Dr. During clarified that pre-clinical data cited has been collected using different AAV-1/2 chimeric vectors in the rodent brain, and studies are ongoing using the vector with the CBA promoter proposed in the protocol. They are now providing additional safety data on their work with rodents to support the Investigational New Drug (IND) submission to the FDA and are working with the proposed vector in marmosets to collect primate data.

Concerning Dr. Bohn's question on the methods for studying resected tissue, in addition to determining NPY expression via PCR and immunocytochemistry, Dr. During said additional sections will be analyzed for markers of cell infiltration and inflammation. Tissue may also be used for electrophysiological studies and NPY release studies using acute slices. The investigators also hope to use electrophysiology to study the excitability of hippocampal slices proximal to the site of injection compared to slices taken at some distance.

Dr. During addressed the possibility of subjects canceling the temporal lobectomy if they receive positive clinical effects from the NPY vector. He noted that, as with any surgical procedure, the patient has the option of changing his or her mind prior to the actual resection. The investigators don't think this is likely because the benefits of resective surgery are extensive and it's unlikely that such benefits will be obtained from the NPY vector. However, they're modifying the protocol to accommodate this possibility. Any subjects who decide against the resection would be monitored closely and told that resective surgery could be scheduled at a future date. In these cases, the trial would otherwise be unchanged, except for the continued monitoring necessary for these patients and scheduled outpatient follow-up by the attending physicians at appropriate intervals.

Also in response to Dr. Bohn, Dr. During explained that if a clear increase in seizure frequency were to occur following the gene transfer and pose a real risk to a patient, a decision could be made to apply the rescue strategy early. The surgery would be performed early only if non-surgical and pharmacological interventions were unable to control the seizures. This would represent a significant adverse event and be reported as such.

As to Dr. Bohn's question on whether the vector might be transported to the contralateral hippocampus where the rescue strategy does not apply, Dr. During said that although this is not generally seen, any residual expression is unlikely to have deleterious effects, as NPY is widely expressed throughout the brain. Addressing Dr. Bohn's concerns that hippocampal sclerosis in the subjects would interfere with

effective vector distribution, Dr. During clarified that subjects with severe sclerosis and neuronal loss would almost invariably show robust MRI changes, thus, would not require the Phase II evaluation required to enroll as a research participant. Some research participants may have some pathology and cell loss, partially reducing the number of target cells. However, the cells that remain should be sufficiently viable and should be transduced.

In response to Dr. Bohn's and Dr. Dewhurst's questions about the CBA promoter, Dr. During explained that this promoter fragment is the same one they used for all their CBA studies, including those recently published. It was also used for all pre-clinical primate studies in support of the investigators' Parkinson's disease gene transfer trial and in the human brain.

Concerning whether PBS is the optimal vehicle for vector delivery, Dr. During noted PBS is well studied and is formulated for clinical use, while many other vehicles are not. The investigators have used it in earlier pre-clinical and clinical studies. Further, the volumes they are perfusing are small. All AAV stocks contain some variable number of empty particles, but this has not been shown to have any deleterious effects on transduction or toxicity. The investigators have not seen any particle aggregation at the proposed titers, or significantly higher titers.

The investigators explained the proposed use of two vector doses at a volume 6 times higher and 10 times more concentrated than in their ongoing Parkinson's trial as necessary because the target region has a much greater volume and a far greater number of target cells than that of the Parkinson's trial.

The 1-month delay between dose cohorts and the 2-week interval between participants is based on the investigators' pre-clinical studies and the protocol in the investigators' Parkinson's trial. Also, the FDA requests that the investigators refrain from enrolling a second participant or moving to the next dose cohort until the peak expression has been reached.

The investigators agreed to modify the informed consent form and protocol to remove the words "gene therapy," which may be misleading and suggest therapeutic benefit (e.g., a reduction in seizures), which is not the purpose of a Phase I study. The investigators will also change the consent form to acknowledge that there may be no benefit from the procedure, that the patient's seizures could get worse, and that there are risks (including sudden unexpected death) associated with the protocol's delay in providing the elective surgery.

In response to Dr. Dewhurst's question on whether pharmacologic agonists of NPY-Y2 receptors exist and have therapeutic potential in the present context, Dr. During noted that this is an area of intensive research by pharmaceutical companies, but that none of the known peptidergic or non-peptidergic compounds has been tested in the clinic. He said such drugs can be predicted to act in all regions of the brain, not only those implicated in seizures, and would influence mood, anxiety, and appetite.

To address Dr. Dewhurst's and Dr. Dichter's questions on whether experiments in spontaneously epileptic rats are necessary before proceeding with a human trial, Dr. During stated that although the investigators are studying chronically epileptic rats in collaboration with Drs. Vezzani and Pitkanen in Finland, these are extremely difficult models to establish and validate. The vast majority of clinically approved and marketed therapies, i.e., anti-epileptic drugs and surgery, were never assessed using such models. In addition, they don't expect that there will be significant differences in transduction in an epileptic versus non-epileptic brain, as the researchers have already investigated gene transfer in human epileptic tissue obtained from temporal lobectomy cases.

Concerning followup results obtained after publication of the *Journal of Neuroscience* article, Dr. During said studies did not continue beyond three months for these specific experiments, however expression levels were stable out to three months.

Addressing the reasons for the high failure rate of drug therapies, Dr. During explained that anti-epileptic drugs are not highly effective, because at the higher doses needed to effectively control the epilepsy, they cause central nervous system side effects that prevent patients from functioning, and in some cases, can

induce comas. Surgery is a better alternative because it's localized to the affected brain region; delivery of a potent molecule to a localized area, as described in the protocol, is also a potentially useful approach.

Addressing the QC procedures for the assays for anti-AAV and anti-NPY antibody detection, Dr. During said the QC procedures to be used will be similar to those used in the investigators' active IND on Parkinson's disease. He stated that they expect to find subjects who are positive for AAV-2 antibodies and will not exclude these subjects. On the issue of the reproducibility of the physical titer and genomic titer assays for AAV, the AAV titration ELISA is a widely used commercially available kit (PRATV, Progen) and is very reproducible. Each kit comes with a calibrated set of AAV standards for generation of a standard curve. The investigators also have a detailed standard operating procedure in place for titering the AAV stocks by quantitative PCR.

Dr. During responded to several other concerns expressed by Dr. Dewhurst, stating that immunodeficient individuals should not be excluded from the study, as the investigators don't believe that recombinant AAV poses any special risks to them. The four Hamilton syringes will be sterilized using combination gas (Freon) and mild heat for sterilization, identical to that used for the Parkinson's trial and for a protocol approved for neurosurgical instruments, which is standard in clinical practice. Dr. During clarified that the investigators have an efficient process for vector production in New Zealand and have generated all their clinical stocks there, as they've found this method to be efficient and cost-effective. Dr. During agreed with Dr. Dewhurst that the consent form statement recommending that sexually active women use contraceptives should be extended to include males as well.

The small number of subjects proposed for the current study (three in each of two-dose cohorts) reflects the difficulty in finding appropriate candidates. The optimal candidates for this protocol, i.e., those with unilateral mesial temporal lobe epilepsy, will usually not require Phase II evaluations. However, the researchers believe they can identify six subjects at UCLA within a 12-18 month period. They also stated that those subjects for whom Phase II evaluation determines a bilateral onset of seizures may still be considered for gene transfer and meet eligibility criteria. Many of these subjects will have been offered unilateral temporal lobectomy despite bilateral seizure onset, and will therefore have the same rescue procedure built in. Because the criteria for selection of candidates for temporal lobectomy after Phase II monitoring are not uniform across epilepsy centers, the protocol will specify in advance which criteria will be used to select research participants.

In response to Dr. Dichter's suggestion that it would be useful to have data from one or more additional species regarding the extent of transduction and the likelihood of spread after injection, the investigators agreed that it would be helpful to have non-human primate data to fully evaluate potential risks. Primate data and human safety data have been obtained for the Parkinson's trial. In March 2004, the researchers presented the RAC with follow-up data on the first cohort of subjects enrolled. They've studied seven subjects, two of whom are beyond their 1-year final follow-up. They've seen no evidence of vector spread, no inflammation or other pathology or complications, and no adverse events relating to the gene transfer. Anecdotal subjects' reports state that they're doing well. This human safety data reduces the need for primate studies. Nevetheless, the researchers have planned a non-human primate study, with the first monkeys to undergo gene transfer shortly. This primate data will help support the IND application and provide more definitive answers relating to spread and transduction efficiencies.

Dr. During addressed several other concerns raised by Dr. Dichter. He stated that the investigators have not observed transduction of glial cells by AAV vectors, including AAV-1, AAV-2, and the chimeric vector using either the NSE promoter or the CBA promoter. On the possible overexpression of NPY in inhibitory interneurons, Dr. During stated that NPY applied to human epileptic hippocampal slices shows appropriate inhibitory responses and no paradoxical excitement. These data strongly suggest that inhibition of inhibitory cells doesn't occur to any appreciable extent.

E. Public Comment

Ms. Karena Cooper, OHRP, asked whether the informed consent document was in its final form, since it did not include the changes discussed at this RAC meeting. Dr. During affirmed that the informed consent document would be undergoing extensive revisions. In addition, the protocol would be changed and additional pre-clinical study data would be added.

F. RAC Recommendations

Dr. Wara summarized the following RAC recommendations:

- To ensure research participant safety, data from the investigators' Parkinson's disease protocol (OBA #0104-469) should be reviewed for any potential safety concerns associated with the doses of and volumes used to deliver the AAV-GAD vector in that trial, since higher doses and volumes are used to deliver the AAV-NPY vector in this trial.

- The investigators should consider completing pre-clinical studies of transgene distribution and toxicity in a chronic epilepsy rat model and in a normal, non-human primate brain with the vector to be used in the clinical trial prior to initiating studies in humans.

- The protocol should specify the criteria to be used by the investigators at UCLA to determine which research participants in the Phase II study will be offered surgical resection.

- The investigators should consider modifying the protocol to allow the accrual of additional research participants to ensure meaningful analysis of sufficient temporal lobe tissue following gene transfer if one or more research participants decide to forego surgical resection.

- The investigators should consider extending the delay between dose cohorts to longer than 1 month and the interval between research participants to longer than 2 weeks to ensure research participant safety.

- Anti-AAV antibody titers in serum should be measured and an assessment of the relationship of the titer to subsequent tissue expression of the transgene should be determined. The potential impact to the risk and benefit of gene transfer should be assessed.

- The endpoints for the study should be clearly defined in the protocol. The investigators should consider modifying the protocol to remove the suggestion that seizure frequency and efficacy of the gene transfer will be formally assessed and the investigators should clearly state that efficacy data will not be obtained from this Phase I study.

G. Committee Motion 2

Dr. Bohn moved and Dr. Gelehrter seconded a motion that the above recommendations be included in the letter to the principal investigators and the sponsor as expressing the comments and concerns of the RAC. The RAC voted to endorse these recommendations with 16 in favor, 0 opposed, 0 abstentions, and 1 recusal (Dr. Bernard Lo).

VI. Closing Remarks and Adjournment/Dr. Wara

Dr. Wara thanked the participants and adjourned the meeting at 11:50 a.m. on September 23, 2004.

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

_____
Stephen M. Rose, Ph.D.
Executive Secretary

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

Date: _____

_____
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Attachment I
Recombinant DNA Advisory Committee Roster

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Attachment II
Public Attendees

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Matthew During, Cornell University
Denise Gavin, FDA
Andy Hawkins, *The Blue Sheet*
Maritza McIntyre, FDA
Mercedes Serabian, FDA
Michael Sorell, Neurologix, Inc.
Daniel Takefman, FDA
Brenda Wong, University of California, San Diego

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
AE	adverse event
AED	antiepileptic drug
CBA	chicken β-actin
CNS	central nervous system
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
NIH	National Institutes of Health
NPY	neuropeptide Y
OBA	NIH Office of Biotechnology Activities
PBS	phosphate-buffered saline
RAC	Recombinant DNA Advisory Committee
SCID	severe combined immunodeficiency disease
TLE	temporal lobe epilepsy
UCLA	University of California, Los Angeles
VNS	vagal nerve stimulation