RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

October 17, 2003

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

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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]

October 17, 2003

The Recombinant DNA Advisory Committee (RAC) was convened for its 93rd meeting at 8:30 a.m. on October 17, 2003, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Theodore Friedmann (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 10:50 a.m. on October 17. The public discussion scheduled for the meeting was original scheduled for the second day of the scheduled September 17-18, 2003, RAC meeting, which was postponed because of weather concerns related to Tropical Storm Isabel. Most RAC members participated in this meeting by teleconference. The following individuals were present for all or part of this meeting, either in person or by teleconference.

Committee Members

W. Emmett Barkley, Howard Hughes Medical Institute *(in person)*
Martha C. Bohn, Northwestern University Medical School *(by teleconference)*
James F. Childress, University of Virginia *(by teleconference)*
Neal A. DeLuca, University of Pittsburgh *(by teleconference)*
David L. DeMets, University of Wisconsin Medical School *(by teleconference)*
Theodore Friedmann, University of California, San Diego *(by teleconference)*
Linda R. Gooding, Emory University *(by teleconference)*
Larry G. Johnson, University of North Carolina, Chapel Hill *(by teleconference)*
Philip R. Johnson, Jr., Columbus Children's Hospital *(by teleconference)*
Terry Kwan, TK Associates *(by teleconference)*
Madison Powers, Georgetown University *(in person)*
David Sidransky, Johns Hopkins University School of Medicine *(by teleconference)*
Robert D. Simari, Mayo Clinic and Foundation *(by teleconference)*

RAC Executive Secretary

Stephen M. Rose, Office of the Director, National Institutes of Health (NIH) *(in person)*

***Ad Hoc* Reviewer**
D. Eugene Redmond, Jr., Yale University *(by teleconference)*

Nonvoting/Agency Representatives
Cynthia A. Rask, U.S. Food and Drug Administration (FDA)
Stephanie L. Simek, FDA

NIH Staff Members
Laurie Lewallen, OD
Marina O'Reilly, OD
Alexander Rakowsky, OD
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[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.

Others

There were 31 attendees at this RAC meeting. A list of RAC members, *ad hoc* reviewers/speakers, and nonvoting/agency liaison representatives is included as Attachment I to this summary. A list of public attendees is included as Attachment II.

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

Dr. Friedmann, RAC Chair, called the meeting to order at 8:30 a.m. on October 17, 2003. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* was published in the *Federal Register* on October 10, 2003 (68 FR 58697-58698). One protocol was reviewed and discussed publicly by the RAC at this meeting.

Dr. Rose reminded RAC members of the rules of conduct governing Special Government Employees, the screening process they undergo before each meeting, and the need to be attentive to conflicts of interest that could arise during the course of the meeting.

II. Discussion of Human Gene Transfer Protocol #0307-593: A Phase I Open-Label Safety Study of Intrastriatal Infusion of Adeno-Associated Virus Encoding Human Aromatic L-Amino Acid Decarboxylase (AAV-hAADC-2) in Subjects With Advanced Parkinson's Disease (AAV-hAADC-2-003)

Principal Investigator:	Michael Aminoff, M.D., D.Sc., University of California, San Francisco
Additional Presenters:	Krys Bankiewicz, M.D., Ph.D.; Philip Starr, M.D., Ph.D.; and Ruth Ryan Lessard, Avigen, Inc.
Sponsor:	Avigen, Inc.
RAC Reviewers:	Drs. Bohn, P. Johnson, and Powers
Ad hoc Reviewer:	D. Eugene Redmond, Jr., M.D., Yale University *(by teleconference)*

Dr. Bohn and Dr. P. Johnson read statements regarding issues that may be considered to contribute to the appearance of conflicts of interest for each. Dr. Bohn stated, "Before I begin my review, I would like to make a disclosure. Dr. Howard Federoff has a grant funded by the National Institute of Neurological Disorders and Stroke (NINDS) for a large multicenter effort in Parkinson's disease (including preclinical and basic research in Parkinson's disease, but there is no clinical trial yet), and Dr. Bankiewicz and I have subcontracts from this grant. Dr. Bankiewicz and I are collaborators in our projects supported by this NINDS grant, but our collaboration does not involve Avigen or the protocol that is under review at his public RAC meeting." Dr. P. Johnson explained his involvement with Targeted Genetics, Inc., a company that also produces AAV vectors for use in clinical trials. He noted, "While none of Targeted Genetics trials are aimed at Parkinson's disease or any other disease of the nervous system, I nonetheless want to disclose that fact that I invented two uses of AAV, commercial scale production of AAV vectors and a vaccine vector that were patented by my institution and licensed to Targeted Genetics. My institution receives royalties from Targeted Genetics and, in turn, I receive a portion of these royalty monies from my institution."

A. Protocol Summary

Parkinson's disease (PD) is the second most common neurological disease after Alzheimer's disease with an estimated incidence of 2 in 1,000 people in the general population and 2 in 100 people older than age 65 years. PD results from a loss of or damage to cells in a section of the brain called the substantia nigra. The brain cells that are lost or damaged are the ones that produce a chemical called dopamine, which is needed for normal control of movement. The symptoms of PD are bradykinesia (slow movement), tremors at rest, rigidity of the muscles, and postural instability.

Standard therapy for PD is based primarily on the treatment of patient symptoms with an oral medicine called levodopa, which crosses into the brain and is converted by a protein called aromatic L-amino acid

decarboxylase (AADC) into dopamine. With disease progression, levodopa becomes less effective at treating PD necessitating higher doses; however, increasing doses of levodopa create uncontrollable dyskinesias and other side effects. Patients with advanced PD have limited noninvasive treatment options. A surgical alternative includes implantation of a deep brain stimulating device to reduce symptoms such as dyskinesia or tremors.

PD is a candidate for gene transfer for several reasons: The decomposition of cells in the substantia nigra is well understood, there is considerable clinical experience and data with medicinal approaches used to treat early stages of PD, and the gene transfer approach can be targeted to an isolated section of the brain. The vector chosen to deliver the AADC gene is derived from the adeno-associated virus (AAV), a virus that normally infects about 80 percent of the population during childhood but doesn't cause disease.

The study proposed is a Phase I dose-escalation study to assess the safety of an AAV vector expressing the human enzyme AADC (AAV-hAADC) when inserted into the brains of participants with advanced PD. Secondary objectives include determination of the dose of AAV-hAADC that most effectively restores normal levels of AADC activity, assessment of the effects of AAV-hAADC on the clinical symptoms of PD, and assessment of the increase or reduction of levodopa taken by participants.

B. Reviews by RAC members and *ad hoc* reviewer

The RAC members voted for in-depth review and public discussion of the protocol. Drs. Lo and Wara recused themselves from initial review of this protocol. RAC reviewers Drs. Bohn, P. Johnson, and Powers and *ad hoc* reviewer Dr. Redmond submitted written reviews, to which the investigators responded in writing and during the meeting.

Dr. Bohn raised several concerns. She was concerned about the possibility that the AAV vector could be transferred in neurons in both retrograde and anterograde directions. Consequently, AADC enzyme activity may be increased in other brain areas such as globus pallidus, cortex, thalamus, or substantia nigra, which could lead to increased dopamine levels in these areas and the effect of this is unclear. If cognitive, hallucinations or other affective disorders should occur as a result of increased dopamine levels in other brain regions, participants might have to be taken off their L-dopa treatment. Dr. Bohn noted that the vector will transduce medium spiny neurons, which normally do not make or store dopamine. Since these cells do not regulate dopamine release, she asked what effect chronic dopamine expression may have on the striatal neurons. Dr. Bohn expressed concern about the lack of a rescue strategy if unexpected effects occur.

Dr. Bohn considered strengths of the proposal to be the ability to control the activity of the transgene by L-dopa administration and to monitor transgene levels by PET imaging. Regarding the clinical design, Dr. Bohn suggested that the dose-escalation plan, which proposes 1 month between cohorts, is too short to observe potential adverse effects caused by the expression of the transgene, particularly in other brain areas. She asked if participants would be screened for titers of neutralizing antibodies to AAV and monitored for AADC antibody levels. Dr. Bohn also noted that the informed consent document stated that the trial is the first for PD, but this information is incorrect thus needs to be changed.

Dr. P. Johnson asked for clarification of the dose of vector to be administered in the trial and the dose escalation scheme. He also asked why significant pre-existing immunity to AAV2 was not an exclusion criterion in this small study with limited numbers of subjects. He asked whether enough is known about the biology of the therapeutic response and the adequacy of the animal model in predicting unanticipated side effects. He asked about the significant lag between detection of transgene expression and a therapeutic effect. Regarding the biodistribution studies, he asked whether vector might be detected outside the brain if a more sensitive assay were used.

Dr. Powers noted that the informed consent document was overly optimistic in tone regarding expectation of benefit and provided too little information about the limitations of non-human animal models and potential therapeutic alternatives. His primary concern was whether the risk-benefit ratio was sufficiently

favorable to proceed with this clinical trial considering the issues raised regarding the adequacy of a rescue strategy and the potential for vector expression in other parts of the brain.

Dr. Redmond expressed concern that the transduced cells expressing AADC would not necessarily be the same cells responsible for "natural" dopamine production and whether the transduced cells would be able to manufacture and regulate dopamine production in the proper manner. He asked how other anti-PD medications may interact with the proposed injections with regard to safety and secondary assessment of efficacy. He recommended that any participant with a history of prior treatment for depression with neuroleptics or antidepressants should be excluded, and that the occurrence of hallucinations should be considered a serious adverse event (SAE) and a dose-limiting toxicity for the dose-escalation study. Participants should be prescreened for significant neutralizing antibody titers to AAV and should be excluded if they are found to have such antibodies. Regarding the risk-benefit ratio, Dr. Redmond noted that this protocol offers a significant and possibly irreversible risk coupled with a small increment in benefit, and many patients have alternative treatments available.

C. RAC Discussion

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

- Dr. Friedmann asked whether the AAV vectors were episomal or integrated in the non-human primate studies and whether the same result would be expected in humans.

- Dr. Redmond noted that the principal advantage of levodopa therapy, compared with dopamine agonist therapy, is that it takes advantage of the internal regulation of the dopamine neuron. If the AADC is producing dopamine in other neurons that do not have that capacity, he wondered what the advantage of this proposed treatment would be, compared with a dopamine agonist that is similarly unregulated.

- Dr. Redmond wondered whether the investigators had demonstrated dyskinesias in non-human primates.

- Dr. P. Johnson asked whether this disease state is so dire that such a highly novel and highly risky therapy is justified.

- Dr. Bohn wondered how closely the animal model mirrors human disease, while also acknowledging that better animal data are not possible at present. Although the data from the non-human primates studies are convincing, some RAC members noted that it is not possible to predict from the non-human primates studies what will happen in humans, and the only rescue strategy should SAEs occur is surgery.

- Dr. Redmond agreed with Dr. Bohn that it would be preferable to have a molecular rescue strategy. However, he asked for more information about the results in the non-human primates studies that suggested that removal of levodopa resulted in recovery from dyskinesias.

D. Investigator Response

Dr. Bankiewicz explained that the cells that are being transduced are striatal neurons expressing dopaminergic receptor; these cells do not degenerate in PD. The same cells that express the receptors could produce the dopamine, which then would bind to those receptors as a local delivery of the agonist. Patients respond to agonists, and response is expected with this local delivery of the agonist. As a consequence of this local production of dopamine and on the basis of observations in animal studies to date, the dose of levodopa would likely be able to be reduced dramatically thereby potentially leading to a reduction in some of the side effects associated with levodopa use.

Dr. Bankiewicz stated that local production of dopamine in the regions most devoid of dopaminergic innervation would most likely balance the dopaminergic innervation in the striatum. Although the

investigators are not proposing in this study that normal brain function will be restored, they are proposing that, by increasing dopaminergic innervation in one part of the basal ganglia, they will be able to stimulate the D1 and D2 receptors, which resulted in dramatic clinical improvement in non-human primates. It is likely that the level of levodopa administration would be reduced dramatically for the study participants.

Dr. Aminoff noted that the benefit of this proposed approach would be to allow a more consistent sustained response to levodopa but at a lower dose that would, therefore, produce many fewer dyskinesias.

Regarding Dr. Redmond's concern about drug interactions, Dr. Aminoff explained that possible interactions with other drugs would be the same as if the research participants were taking levodopa, so that, for example, investigators will warn research participants to avoid taking nonselective monoaminoxydase inhibitors.

Dr. Starr noted that deep brain stimulation is an alternative surgery for this group of potential participants. Having performed many such surgeries, he explained the complexity of maintaining these patients' hardware in good working order. The rate of repeat surgeries for hardware complications is significant, so deep brain stimulation is not considered the surgical answer to PD.

In response to Dr. Redmond's concerns about the potential for dyskinesias and hallucinations, Dr. Bankiewicz noted that in animals that were not given the gene transfer product, increasing levels of levodopa did indeed lead to these side effects. In the AADC-treated animals, the dose of levodopa could be reduced significantly so that dyskinesias and hallucinations were not seen. Dr. Bankiewicz further noted that in the non-human studies using tissue transplants of dopaminergic cells (in preparation for the human fetal dopaminergic cell trials) no evidence of unregulated levels of dopamine were noted.

Regarding dosing, Dr. Aminoff noted the need for more evidence from a current non-human primate study. These discussions are under way between the FDA and Avigen. Evidence from this ongoing non-human primate study will help determine the human dose for this proposed protocol.

To address the issue of what happens when medial striatal neurons chronically make high levels of dopamine, Dr. Bankiewicz explained that the investigators placed rodents and non-human primates on chronic administration of levodopa. Since the gene transfer was unilateral, investigators were able to compare the identity of new cells in the two hemispheres of the animals' brains. They found exactly the same number of cells in both hemispheres, despite the fact that one side had not been targeted by AADC. This result suggests that the medial striatal neurons were not depleted in the animals, even at different time points. In other animal experiments that included more focal AADC expression, the animals were placed on a chronic regimen of levodopa. Results indicated that the cells in the area of the brain that was known to produce large quantities of dopamine were identical to cells in the area of the brain that was not transduced.

In response to concerns expressed by several RAC members, Dr. Starr discussed the availability of rescue strategies. For all of the currently imaginable complications that could occur, effective surgical solutions exist. The dyskinesias are easy to treat with either ablation or stimulation. If there is a problem with the vector such that these participants can no longer receive levodopa because of some complication other than dyskinesias, these individuals still have the option of subthalamic surgery, which can suppress symptoms in the absence of levodopa. The surgical rescue strategies are straightforward, although they do involve another surgery.

In response to several comments about building in tissue specificity or a molecular on/off switch that might serve as a regulatory switch, Dr. Bankiewicz acknowledged that such an arrangement would provide an additional level of assurance that the expression could be turned off. With further development of the vector, it may be possible to incorporate such a regulatory arrangement, but it would require a lot of testing to ensure that those systems are not toxic to the brain and that the drugs regulating gene expression do not have dose effects in humans.

Dr. Bankiewicz described a study performed by him and his colleagues that addressed some of the concerns raised by several RAC reviewers regarding the dyskinesia effects seen after fetal transplant in patients. In one of the non-human primate studies, the investigators tried to mimic a mechanism that was seen in the fetal transplants that expressed AADC in focal areas of the non-human primates striatum. Those animals developed pronounced dyskinesias in response to levodopa, suggesting that there is a focal production of dopamine that would make them more prone to dyskinesias. Dr. Bohn asked what is meant by "focal production" and Dr. Bankiewicz responded that there appeared to be "hot spots" within the striatum that, if transduced with the AADC transgene and then given levodopa, would lead to the development of dyskinesias.

Regarding Dr. P. Johnson's concern about the calf serum, Ms. Lessard stated that all of the materials used for the manufacturing procedure are audited and monitored through a quality system, and qualified vendors supply the fetal calf serum.

Dr. Aminoff elaborated on the clinical status of PD patients who have stage III or IV disease, the proposed stages for this protocol. He noted that these patients have a very disabling disease which limits their daily functioning and who are reaching the end of their available therapeutic options.

E. Public Comments

No comments were received from the public.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations:

Scientific/Medical/Study Design Issues

- The incomplete understanding of the basic biological mechanisms and safety of inducing chronic production of dopamine in striatal neurons is a concern. However, because the preclinical animal studies done to date are as complete as can be expected for this phase of development, proceeding with a phase I safety study at this time is not unwarranted.
- The risk associated with delivering transgenes to a significant number of neurons without having an adequate method of removing them is a concern. Because the rescue strategies proposed in the study (such as stopping the use of L-dopa or surgically resecting the transduced area) carry risks of their own, the application of more sophisticated molecular approaches should be considered as they become available for human use.
- The period of time between dosing cohorts should be extended beyond the proposed 30 days in order to enhance monitoring of unexpected adverse effects of the vector.
- Criteria need to be established for screening subjects for levels of neutralizing antibody against AAV. Subjects found to have significant antibody titers against AAV should be excluded from the study.
- Consideration should be given to redefining the exclusion criteria of depression and the current or prior use of anti-depressant therapies to ensure that subjects with a past history of depression are excluded from participation.
- The exclusion criterion of prior neurosurgery should be more precisely defined.
- The histology results from ongoing non-human primate studies should be submitted to NIH OBA.

Ethical/Legal/Social Issues

The investigators should confer with their Institutional Review Board (IRB) about any recommended changes to the informed consent documents and process.

The changes that were made to the informed consent document between initial review and public review were acknowledged and viewed favorably. However, further refinements to the informed consent document are needed, particularly in the following areas:

- The statement that the protocol is the first neurologic gene transfer study for Parkinson's disease is inaccurate and should be deleted.
- Further information is needed about the novelty of the product and the protocol's design and the potential for complications.
- Less emphasis should be placed on the potential benefits of the approach.
- A clear statement in lay terms is needed explaining that once the product is injected into the brain, it may not be possible to remove it safely.

G. Committee Motion 1

It was moved by Dr. L. Johnson and seconded by Dr. Bohn that these recommendations expressed the comments and concerns of the RAC. The vote was 12 in favor, 0 opposed, 2 recusals and 0 abstentions.

III. Adjournment/Dr. Friedmann

Dr. Friedmann noted that Protocol #592, originally scheduled to be discussed on Day Two of the September 2003 RAC meeting, had been postponed to be discussed at the December 2003 RAC meeting. He adjourned this RAC meeting at 10:50 a.m. on October 17, 2003.

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

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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:

_____
Theodore Friedmann, M.D.
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Attachment I
RAC Roster
Recombinant Dna Advisory Committee

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Attachment II
Public Attendees

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Theresa Chen, FDA
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Susan Liebenhart, FDA
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Mercedes Serabian, FDA

Attachment III
Abbreviations and Acronyms

AADC	aromatic L-amino acid decarboxylase
AAV	adeno-associated virus
AAV-hAADC-2	adeno-associated virus encoding human aromatic l-amino acid decarboxylase
PD	Parkinson's disease
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event