
RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 16-17, 2009

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

Contents

I.	Day 1 Call to Order and Opening Remarks.....	2
II.	Gene Transfer Safety Assessment Board Report and Discussion of Observation of a Clonal Population of Cells in a European Trial: Lentiviral Vector Containing β -Globin Gene for β -Thalassemia	2
III.	Discussion of Human Gene Transfer Protocol #0904-977: Direct Central Nervous System Administration of a Replication-Deficient, Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human CLN2 cDNA to Children with Late Infantile Neuronal Ceroid Lipofuscinosis	3
	A. Protocol Summary	3
	B. Written Reviews by RAC Members	4
	C. RAC Discussion	5
	D. Investigator Response	6
	1. Written Responses to RAC Reviews	6
	2. Responses to RAC Discussion Questions.....	7
	E. Public Comment.....	8
	F. Synopsis of RAC Discussion and RAC Observations and Recommendations.....	8
	G. Committee Motion 1.....	9
IV.	Biosafety Considerations for the Cloning of the Risk Group 4 Mononegavirales (Marburg, Nipah, and Hendra Viruses) in Nonpathogenic <i>E. coli</i>	9
	A. Presentation by Dr. Feldmann	9
	B. Presentation by Dr. Dr. Buchmeier	9
	C. RAC Discussion	10
	D. Public Comment.....	11
	E. Committee Motion 2.....	11
V.	Day 1 Adjournment.....	11
VI.	Day 2 Call to Order and Opening Remarks.....	12
VII.	Minutes of the March 3-4, 2009, RAC Meeting	12
	A. Committee Motion 3	12
VIII.	Certificates of Appreciation for RAC Member Service to the NIH	12
IX.	Discussion of Human Gene Transfer Protocol #0904-975: A Phase I Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Replication-Defective HIV-1 Vaccine (HIVAX™) in HIV-1 Infected Subjects Receiving Highly Active Antiretroviral Therapy	12
	A. Protocol Summary	12
	B. Written Reviews by RAC Members	13
	C. RAC Discussion	14
	D. Investigator Response	14
	1. Written Responses to RAC Reviews	14
	2. Responses to RAC Discussion Questions.....	15
	E. Public Comment.....	16
	F. Synopsis of RAC Discussion and RAC Observations and Recommendations.....	16
	G. Committee Motion 4.....	17

X.	Discussion of Human Gene Transfer Protocol #0904-981: A Phase I/II Trial Assessing the Safety and Efficacy of Bilateral Intraputamenal and Intranigral Administration of CERE-120 AAV-2-Neurturin in Subjects with Idiopathic Parkinson’s Disease	18
A.	Protocol Summary	18
B.	Written Reviews by RAC Members	19
C.	RAC Discussion	21
D.	Investigator Responses	21
1.	Written Responses to RAC Reviews	21
2.	Responses to RAC Discussion Questions.....	24
E.	Public Comment.....	25
F.	Synopsis of RAC Discussion and RAC Observations and Recommendations.....	25
G.	Committee Motion 5.....	27
XI.	Discussion of Human Gene Transfer Protocol #0904-976: A Phase I Ascending-Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent Glioblastoma Multiforme.....	27
A.	Protocol Summary	27
B.	Written Reviews by RAC Members	28
C.	RAC Discussion	29
D.	Investigator Response	29
1.	Written Responses to RAC Reviews	29
2.	Responses to RAC Discussion Questions.....	30
E.	Public Comment.....	30
F.	Synopsis of RAC Discussion and RAC Observations and Recommendations.....	30
G.	Committee Motion 6.....	31
XII.	Closing Remarks and Adjournment	31
Attachment I.	Recombinant DNA Advisory Committee Roster	A-I-1
Attachment II.	Public Attendees	A-II-1
Attachment III.	Abbreviations and Acronyms	A-III-1

[Note: The latest Human Gene Transfer Protocol List can be found at the Office of Biotechnology Activities’ Web site at <http://oba.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 Meeting¹**

June 16-17, 2009

The Recombinant DNA Advisory Committee (RAC) was convened for its 117th meeting at 1:50 p.m. on June 16, 2009, at the National Institutes of Health (NIH), Conference Room 6, Building 31-C, Bethesda, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 1:50 p.m. until 5:20 p.m. on June 16 and from 8:20 a.m. until 3:00 p.m. on June 17. The following individuals were present for all or part of the June 2009 RAC meeting.

Committee Members

Jeffrey S. Bartlett, Nationwide Children's Hospital/The Ohio State University
Michael J. Buchmeier, University of California, Irvine
Hildegund C.J. Ertl, The Wistar Institute/University of Pennsylvania
Hung Y. Fan, University of California, Irvine
Howard J. Federoff, Georgetown University Medical Center
Jane Flint, Princeton University
Jeffrey P. Kahn, University of Minnesota (*via teleconference on Day 2 only*)
Joseph A. Kanabrocki, The University of Chicago (*present on Day 2 only*)
Louis V. Kirchhoff, University of Iowa
Bernard Roizman, The University of Chicago
Prediman K. Shah, Cedars-Sinai Medical Center (*via teleconference*)
Robyn S. Shapiro, Drinker, Biddle and Reath
Nikunj V. Somia, University of Minnesota, Twin Cities
Lee-Jen Wei, Harvard University
David A. Williams, Children's Hospital Boston/Harvard Medical School (*via teleconference*)
James R. Yankaskas, The University of North Carolina at Chapel Hill
John A. Zaia, City of Hope (*via teleconference*)

Office of Biotechnology Activities (OBA)

Jacqueline Corrigan-Curay, Office of the Director (OD), NIH

Ad Hoc Presenters and Speakers

Thomas Arminio, National Institute of Allergy and Infectious Diseases (NIAID), NIH (*via teleconference on Day 1*)
Marshall Bloom, NIAID, NIH (*via teleconference on Day 1*)
Ellen Wright Clayton, Center for Biomedical Ethics and Society (*via teleconference on Day 1*)
Hideki Ebihara, NIAID, NIH (*via teleconference on Day 1*)
John D. Elsworth, Yale University School of Medicine (*present on Day 2 only*)
Heinrich Feldmann, NIAID, NIH (*via teleconference on Day 1*)
Thomas B. Freeman, University of South Florida (*present on Day 2 only*)
Lawrence A. Tabak, National Institute of Dental and Craniofacial Research (NIDCR), NIH (*present on Day 1 only*)

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.

Nonvoting Agency Representatives

Kristina C. Borrer, 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/OD/OBA Staff Members

Linda Gargiulo
Bob Jambou
Laurie Lewallen
Maureen Montgomery
Marina O'Reilly
Gene Rosenthal
Tom Shih
Mona Siddiqui

Attendees

There were 75 attendees at this 2-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 this document.

I. Day 1 Call to Order and Opening Remarks

Dr. Federoff, RAC Chair, called the meeting to order at 1:50 p.m. on June 16, 2009. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on May 27, 2009 (74 FR 25248). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (GTSAB), a subcommittee of the RAC, public review and discussion of four protocols, discussion of observation in European trial of a clonal population of cells of lentiviral vector containing β -globin gene for β -thalassemia, and biosafety considerations for the cloning of the Risk Group 4 Mononegavirales (Marburg, Nipah, and Hendra viruses) in nonpathogenic *E. coli*.

Dr. Corrigan-Curay reminded RAC members of the rules of conduct that apply to them as special Federal Government employees, read into the record the conflict of interest statement, and suggested that related questions be addressed to the OBA committee management officer.

II. Gene Transfer Safety Assessment Board Report and Discussion of Observation of a Clonal Population of Cells in a European Trial: Lentiviral Vector Containing β -Globin Gene for β -Thalassemia

RAC Reviewers: Drs. Federoff, Strome, Williams, Yankaskas, and Zaia

Dr. Williams presided over a short discussion of the observation, from a European trial, of a clonal population of cells transduced with a lentiviral vector expressing the β -globin gene for β -thalassemia. The GTSAB received information on a laboratory finding on a French gene transfer trial for sickle cell anemia and β -thalassemia. The investigators use CD34+ cells transduced by a lentiviral vector containing the β -globin gene under the control of a β -globin promoter. According to a press release by the French Medicine Agency (Agence Francaise de Securite Sanitaire des Produits de Sante [AFSSAPS]), a "relative

clonal dominance” was detected in a research participant with β -thalassemia major 2 years after that participant received genetically modified hematopoietic stem cells. The clonal population shares a common integration site in a gene coding for the protein HMGA2, which is associated with both benign and malignant tumors. The clonal population of cells was detected 5 months ago and has remained stable since then, and the clinical status of this individual has not changed. Prior to gene transfer administration, this individual required blood transfusions once a month, on average. Since the gene transfer administration, this individual has not required transfusions for more than 11 months. The trial investigators are performing additional studies to evaluate the consequences of this integration and the capacity of the cells to proliferate. Thus far, only two participants in that trial have received the gene-modified cells. Until these studies are completed and reviewed by the AFSSAPS, which is scheduled to occur in September 2009, no additional individuals will receive the gene-modified cells.

The OBA notified investigators in gene transfer trials using lentiviral vectors and retroviral vectors in hematopoietic or other stem cells about this event. When additional data about this event become available, the GTSAB will provide an update to the RAC.

Dr. Williams reported that of the 14 protocol submissions received by the OBA in the past 3 months, 10 were not selected for public review at this RAC meeting; 9 were for cancer, and 1 was a vaccine study for human immunodeficiency virus (HIV). A total of 13 trials, all of which were for cancer, began enrolling research participants. Annual reports submitted included those for a number of trials showing positive results. Protocol #0212-563, “Administration of Peripheral Blood T-Cells and EBV Specific CTLs Transduced to Express GD-2 Specific Chimeric T-Cell Receptors to Patients with Neuroblastoma,” used engineered Epstein-Barr virus-specific cytotoxic T cells (CTLs) to express a chimeric antigen receptor directed to disialoganglioside GD2, a nonviral tumor-associated antigen expressed by human neuroblastoma cells. In the November 2, 2008, online issue of *Nature Medicine*, the investigators reported that “Infusion of these genetically modified cells seemed safe and was associated with tumor regression or necrosis in half of the participants tested. Hence, virus-specific CTLs can be modified to function as tumor-directed effector cells.” (<http://www.nature.com/nm/journal/v14/n11/full/nm.1882.html>)

Dr. Zaia discussed the adverse events (AEs) that were reported to the OBA during this reporting period. Of the 37 events reviewed by the GTSAB, two were discussed briefly, both of which involved the deaths of research participants who received T-cell infusions. The final conclusion of the GTSAB was that the deaths were not a direct consequence of gene transfer. Questions remain about the underlying causes of both events, and it is possible that a lower starting dose and slower dose escalation might be warranted in these two trials.

III. Discussion of Human Gene Transfer Protocol #0904-977: Direct Central Nervous System Administration of a Replication-Deficient, Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human CLN2 cDNA to Children with Late Infantile Neuronal Ceroid Lipofuscinosis

Principal Investigator:	Ronald G. Crystal, M.D., Weill Medical College, Cornell University
Sponsor:	Ronald G. Crystal, M.D.
RAC Reviewers:	Drs. Bartlett, Federoff, and Flint
<i>Ad hoc</i> Reviewer:	Ellen Wright Clayton, M.D., J.D., Vanderbilt University School of Law

A. Protocol Summary

Late infantile neuronal ceroid lipofuscinosis (LINCL) is an inherited, childhood neurodegenerative lysosomal storage disease that results in cognitive and motor impairment and early death by ages 10 to 12 years. LINCL follows an autosomal recessive pattern of inheritance involving mutations in the CLN2 gene that codes for tripeptidyl peptidase (TPP-1), a proteolytic enzyme. Deficiency of TPP-1 leads to the progressive accumulation of autofluorescent lipopigments known as ceroid-lipofuscin. This leads to death of the nerve cells in the brain and progressive loss of brain function. Although there is no current cure for LINCL, this clinical study will evaluate the concept that persistent expression of the normal CLN2 complementary deoxyribonucleic acid (cDNA) in the central nervous system (CNS) will result in the

production of sufficient amounts of TPP-1 to prevent additional loss of neurons and hence limit disease progression. To assess this concept, an adeno-associated virus (AAV) serotype rh.10 gene transfer vector (AAVrh.10_{CU}hCLN2) will be used to transfer the CLN2 cDNA, coding for TPP-1 protein, to the brain of children with LINCL.

Previous clinical data from this laboratory using a lower dose and a less efficient delivery system to the CNS (AAV human serotype 2 [AAV-2]) provided evidence that AAV-mediated gene transfer may have phenotypic impact on progression of the disease. Preclinical data show the AAVrh.10 delivery system to be considerably more effective than AAV-2 in animal models, providing enhanced performance and survival when administered to the CNS of CLN2 knockout mice. Additional preclinical studies with administration of this vector directly to the cortex of nonhuman primates have demonstrated the general safety and absence of behavioral impact. Based on these data, the investigators propose a clinical trial for 16 children with LINCL, all with early disease, with an ascending-dose design with the AAVrh.10_{CU}hCLN2 vector compared with a parallel, untreated control group. The primary aims of the study are to (1) assess the hypothesis that direct administration of AAVrh.10_{CU}hCLN2 to the brain of children with LINCL can be achieved safely and with minimal toxicity and to establish the antivector and antitransgene immune response to administration, and (2) within the constraint of a study design focused on safety, evaluate the hypothesis that direct administration of AAVrh.10_{CU}hCLN2 to the brain of children with LINCL will slow down or halt progression of the disease as assessed by neurological rating scales and quantitative magnetic resonance imaging (MRI). All study individuals will be monitored before and after vector administration with a variety of safety measures.

The primary efficacy parameters will be (1) the Weill Cornell LINCL scale, a comprehensive clinical disease severity rating scale focused on the CNS dysfunction that characterizes the progressive deterioration of this disorder, with sufficient discriminatory parameters to capture the impact of treatment; (2) the Child Health Questionnaire quality of life scale; (3) the Mullen developmental psychological assessment; and (4) the United Batten Disease Rating Scale (developed by Mink et al. for the juvenile-type of neuronal ceroid lipofuscinosis). The secondary efficacy parameters will be derived from MRI measures including percentage of grey matter volume, percentage of ventricular volume, and cortical apparent diffusion coefficient, the three parameters that correlate best with LINCL CNS deterioration.

B. Written Reviews by RAC Members

Nine RAC members voted for indepth review and public discussion of this protocol. Key issues included the importance of public discussion of the safety of using this novel AAV vector in this vulnerable pediatric population, the safety of the proposed dose escalation, and the rationale for enrolling a population with early disease.

Three RAC members and one *ad hoc* reviewer provided written reviews of this proposed trial.

Dr. Bartlett asked the investigators to explain how they would ensure equal and unbiased enrollment, given the statement in the protocol that the families would have a choice as to whether to be included in the control arm or the gene transfer arm of this protocol. He requested that the investigators state their goals for this proposed trial and detail how the revised outcome measures would ensure a more definitive assessment of efficacy in this protocol compared with the prior AAV-2 protocol. Dr. Bartlett asked the investigators to discuss whether they had considered or evaluated other possible vector delivery strategies, whether other AAV capsids had been assessed for gene transfer in the CNS, how the injection volume of the rh.10-based vector would differ from the prior study, whether serum neutralizing antibody or the presence of an anti-AAVrh.10 cellular immune response at prescreening would serve as an exclusion criterion, and whether an anti-TPP-1 response had been observed in the prior trial. Regarding the preclinical experiments, Dr. Bartlett queried whether the investigators had data on the longevity of TPP-1 expression in the CLN2^{-/-} mice, why all of those mice eventually succumbed to disease, and whether immunological responses could explain the lower variability in disease manifestation in animals treated at earlier time points and how that information might affect the rationale for dosing children with early-stage disease.

Noting that dose titration was not performed in nonhuman primates, Dr. Federoff asked the investigators to comment on the doses selected for this trial and the expected relationship between the low- and high-dose cohorts and the anticipated levels of TPP-1. He requested comment on the finding of spongiosis in the nonhuman primate CNS studies, whether the peripheral vector detected in the rat biodistribution studies would elicit an immune response in children, and whether the stopping rules would be made more explicit because the serious adverse events (SAEs) in the prior trial could not be linked definitively to either the vector or the procedure. Dr. Federoff inquired about additional data on immunological studies from the prior Phase I AAV-2 trial with respect to the TPP-1 gene product, histological and molecular expression data from the nonhuman primate study involving AAVrh.10-TPP-1, and the use of the two-stage delivery methodology proposed for this trial.

Dr. Flint asked the investigators to describe the rationale for extrapolating the properties of a vector with a nonhuman virus capsid in animal models to the concept that AAVrh.10_{CU}hCLN2 would transduce human neurons far more efficiently than the vector with the AAV-2 capsid. She wondered whether the investigators had considered the possibility that a neuron-specific promoter might result in higher levels of expression of the CLN2 transgene. Dr. Flint requested an explanation of the rationale for the proposed more than fourfold increase in vector dose rather than using a more conservative approach.

Ad hoc reviewer Dr. Clayton asked why the description of risks in the protocol and in the informed consent document differs from the more extensive list of adverse reactions listed by other investigators. She wondered why the risk of developing immunity to AAV was not mentioned in the protocol. Dr. Clayton expressed concern that the description of benefit was confusing; she asked the investigators to clarify whether this protocol was expected to show no benefit or whether they expected a possible slowing of decline based on the earlier clinical trial.

C. RAC Discussion

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

- Dr. Ertl noted that this vector is more immunogenic than AAV-2 and that the investigators will be dosing children who are likely to be AAV naive. If those child participants should acquire a natural AAV infection with an adenovirus, they could develop a significant T-cell response. She recommended the investigators watch for development of that response.
- Dr. Ertl asked whether these children have a normal immune system.
- Dr. Wei queried whether it would be possible for the investigators to obtain data from a similar trial in Germany, to combine data so both trials would benefit from data showing a temporal effect.
- Dr. Wei suggested that the investigators reconsider using an adaptive trial design, as doing so might allow them to take advantage of early signals of safety or efficacy.
- Noting that the level and duration of expression of the transgenes in the animal data were impressive for several months, Dr. Yankaskas wondered what was learned about the level of transgene expression from the participant in the prior trial who died of seizures. He asked how the investigators foresee answering those questions in the future as this protocol develops.
- Both Dr. Clayton and Dr. Ertl encouraged the investigators to contact the German funding agency to find out whether the prohibition against sharing data still exists, as the German investigators may be misinformed about that prohibition, and sharing of data would be a significant enhancement to the research being conducted.

D. Investigator Response

1. Written Responses to RAC Reviews

In response to Dr. Bartlett's question about ensuring unbiased enrollment, the investigators acknowledged the challenge. Based on the prior AAV-2-based trial, there is not enough time for followup to establish a valid baseline of rate of decline to use the participants as their own controls, and using historic controls is a challenge because of the differences in the clinical rating scales used. The investigators concluded that giving the families the choice is the best strategy. The experience in the AAV-2 trial is that 25 percent to 40 percent of the families decide not to participate in the gene transfer trial. The investigators cannot guarantee "equal and unbiased enrollment" but believe it is the best control group, given the ethical issues.

The investigators stated that the goals of the trial are to assess safety and obtain as much efficacy information as possible, given the limitations in available participants and the ethical issues involved, and that the primary outcome measures use the best clinical assessment instruments available. The secondary outcome parameters are the state-of-the-art MRI parameters for LINCL as described in published articles.

Regarding other possible vector delivery strategies, although other routes and strategies were considered, the investigators deemed that direct administration was the best strategy for LINCL. Using the AAVrh.10_{CU}hCLN2 vector in nonhuman primates, delivery of the TPP-1 protein to greater than 30 percent of the brain was achieved. The investigators also assessed a number of other natural and engineered AAV vectors, including AAV-7, AAV-9, and AAV-6.2. However, for the human CLN2 cDNA, AAVrh.10 is currently the most effective in mice and is also effective in monkeys (some had prior antivector immunity). It is theorized that human antivector immunity levels, although possible, will likely be absent or low.

The possible relationships among preexisting serum titer, cellular immunity, and gene transfer efficiency are unknown and probably not well modeled for humans by inbred mice. However, given successful transgene expression in monkeys with preexisting anti-AAVrh.10 immunity without significant adverse effects, the investigators do not propose to use preexisting immunity as an exclusion criterion.

In the mice studies, TPP-1 activities were determined at death and were persistent in all groups regardless of injection age and survival time. Therefore, anti-transgene immunity is a less likely explanation. Based on these data, the longevity of expression is at least 18 months (the age at death of the longest surviving mice). The investigators are unsure as to why the neonatal treated mice eventually die, but factors to be considered include the fact that all of the brain may not have been rescued and/or that other organs could become involved if the brain is spared. The primary rationale for treating the children early is to preserve CNS function, as the therapy is expected to stabilize disease but not enhance function.

For determination of dose, the decision was made to lower the first dose to 7.5×10^{10} genome copies (gc)/site (total dose 9.0×10^{11} gc) for the first eight participants; if no safety concerns are observed, then the dose would be raised to 1.5×10^{11} gc/site (the highest dose in the nonhuman primates), for a total dose of 1.8×10^{12} gc in the second cohort of eight participants. At the highest dose, 30 percent of the nonhuman primate brain has TPP-1 levels that are two standard deviations above background. With this dose, it is likely that spread will occur significantly beyond this area at levels that are therapeutic (5 percent to 10 percent of normal levels).

The spongiosis was localized to the administration site, also was seen in the controls, and was likely due to local trauma from the catheter placement.

Anticapsid neutralizing antibody levels were measured and have been published. Prior to gene transfer, no participants had detectable serum anti-AAV-2 neutralizing antibodies. Of the 10 participants, 4 (3 with severe disease, 1 with moderate disease) developed a mild humoral immune response to the AAV-2 capsid following CNS administration of the AAVrh.10_{CU}hCLN2 vector. In no participant did the anti-AAV neutralizing titer rise to greater than 270. Two of the four participants who developed detectable anti-AAV-2 antibodies responded within 1 month, and the other two participants showed a delayed response

that was not observed until 6 months postdosing. For three of the four participants who developed anti-AAV-2 antibodies, the titers returned to baseline by 18 months following gene transfer, remaining mildly elevated in only one participant. Thus, CNS administration of the AAVrh.10_{CU}hCLN2 vector to this population results in only a mild, mostly transient systemic antivector humoral immune response. T-cell studies were not performed in the investigators' prior trial; in the present study, the protocol includes collection of mononuclear cells that will be reserved for the purpose of assessing anticapsid and/or antitransgene immunity as necessary.

The goal of administration to two depths is to obtain maximal administration per burr hole in a fashion that is safe and keeps within the limits of safe total anesthesia time. The strongest supporting evidence that the approach is safe and reasonable is the outcome data on safety and the small but significant impact on neurological status from the first clinical trial with AAV-2.

In terms of stopping rules, every SAE, including death, will be evaluated by the Data and Safety Monitoring Board (DSMB). The DSMB will advise the principal investigator (PI) whether mortality data or adverse event data show it is not ethical to continue to enroll participants. Independent of the DSMB, for all participants, after the 1-month postdrug period, a stopping rule will be implemented based on SAEs related to the administration. SAEs such as death, prolonged intubation (greater than two per week), and/or serious events specifically related to the drug (such as seizure, increased myoclonus, respiratory failure) are sufficient cause to stop the study.

Experiments have not been performed to compare the efficiency of delivery of the transgene to human cells in culture, including neurons. However, the AAVrh.10 vector transduces mouse, rat, and monkey brain much better *in vivo* than does AAV-2. As neurons are primarily at risk with LINCL, it was important to show that transduction with AAVrh.10 vectors resulted in TPP-1 activity in neurons *in vivo*.

The investigators tested multiple promoters, including cytomegalovirus (CMV), neuron-specific enolase with and without the woodchuck hepatitis virus posttranscriptional regulatory element, and elongation factor 1 and phosphoglycerate kinase. They concluded that the CAG promoter, with these vectors and transgene, has been the best for *in vivo* CNS transduction. The expression levels seen in mice with the AAVrh.10 vector and the CAG promoter in conjunction with the survival effects and the dose scale-up calculation suggest that the CAG promoter is suitable for the human study.

2. Responses to RAC Discussion Questions

Acknowledging that the proposed vector is more immunogenic than AAV-2 and that AAV-naive children will likely be dosed, Dr. Crystal agreed to monitor participants closely for the possibility of a natural AAV infection with an adenovirus that would result in a significant T-cell response.

Regarding the normalcy of participants' immune systems, Dr. Crystal explained that there is an absence of data on the immune systems of these children but that no evidence exists that they react abnormally to infections.

Dr. Crystal requested the raw data from a similar trial in Germany, with the goal of combining data to understand the natural history of the disease. When he and his colleagues were developing their study, they sent all their clinical data to the research group in Germany. The German investigators wrote back and said they would like to share their data but that German law would not permit them to do so, even though the data are anonymous.

Regarding the participant who died from seizures in the prior trial, Dr. Crystal explained that the child was in the intensive care unit for a period of time, and after it was obvious that the child was going to die, the family, who is from Britain, decided to take the child home. The child died about 15 days later. Despite the investigators having talked to the family about autopsy, they decided not to have an autopsy performed, so data from that research participant are not available.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Clinical/Trial Design Issues

- For several reasons, the participants are at higher risk of a heightened immune response that could lead to an SAE. First, the study population is younger and may not have been exposed to a naturally acquired AAV infection. Second, the rhAAV vector may induce higher transgene product-specific immune responses compared with the poorly immunogenic AAV-2 vector. If, after vector infusion, the participants are exposed to natural adenoviral infection and concomitantly infected with a wildtype AAV, they could mount a strong T-cell response against the AAVrh.10 as well. As such, participants who develop a febrile illness within 3 months of dosing should be monitored vigilantly.
- Although preclinical data in CLN2-/- mouse models demonstrated a significant increase in survival after administration of the vector construct, the effect was short lived, and the mice ultimately died. The decline in survival was precipitous, although the investigators believe the cause was secondary to the vector's failure to diffuse into critical areas of the brain stem and cerebellum. To optimize vector delivery, neurosurgeons should be consulted about whether stereotactic optimization could enhance the distribution of the transgene product to the brainstem and cerebellum.
- Children with LINCL have progressive neurological decline. As such, it will be difficult to distinguish whether an SAE is attributable to underlying disease or to the surgery and/or vector administration. Data from electroencephalogram monitoring within 24 hours and 2 weeks postinfusion and monitoring of serum antiseizure medication levels are already included in the protocol and should help differentiate between adverse effects of the study and underlying disease. A DSMB will be formed to monitor the study. Nonetheless, every available practical measure that does not further increase the risk to the participant should be employed to discern the potential role of the vector or administration procedure in an AE.

Ethical/Legal/Social Issue

- The article by Arkin and colleagues that was provided as part of the response to the initial RAC review detailed several procedural steps that are to be taken to enhance the informed consent process. For example, the PI will not be involved in the clinical care of participants in the trial, and to minimize the therapeutic misconception, a consent monitor is expected to ask the parents to restate their understanding that they are granting permission for their child to be involved in an experimental study that is not designed to benefit their child. The measures outlined in this article (<http://www.liebertonline.com/doi/abs/10.1089/hum.2005.16.1028>) belong in the protocol.

G. Committee Motion 1

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Although no official motion was made or seconded, Dr. Federoff asked that the RAC approve these summarized recommendations. The vote was 14 in favor, 1 opposed, 0 abstentions, and 0 recusals.

Dr. Wei voted against the recommendations because, in his view, they did not go far enough in raising concerns about the study design, particularly the two-dose escalation design. To maximize the chance of reaching an efficacious dose safely, Dr. Wei suggested that an adaptive study design be considered,

using a more traditional sequential dose escalation, with three participants per cohort. The ability to implement such a design would be contingent on obtaining previous safety and temporal efficacy data from a similar study conducted in Germany.

IV. Biosafety Considerations for the Cloning of the Risk Group 4 Mononegavirales (Marburg, Nipah, and Hendra Viruses) in Nonpathogenic *E. coli*

- Speakers: Michael J. Buchmeier, Ph.D., M.S., and Heinrich Feldmann, M.D., Ph.D., Rocky Mountain Laboratories (RML), NIAID, NIH (*via teleconference*)
- Participants: Thomas Arminio, R.N., M.P.H., RML, NIAID, NIH (*via teleconference*); Christopher C. Broder, Ph.D., M.S., Uniformed Services University of the Health Sciences; Capt. Jody Luke, RML, NIAID, NIH (*via teleconference*); Hideki Ebihara, Ph.D., RML, NIAID, NIH (*via teleconference*); Nancy P. Hoe, Ph.D., RML, NIAID, NIH (*via teleconference*)

A. Presentation by Dr. Feldmann

Dr. Feldmann discussed the mission, objectives, and program mandates of the RML Laboratory of Virology program and presented an overview of its structure and personnel and a floor plan of the high-containment area. Infectious virus research will be conducted in high containment, and rescues of these clones will be conducted in biosafety level 4 (BL4); related animal research will be conducted in animal BL4.

The program's research interests include understanding:

- Pathogen (viruses) life cycle to identify targets for intervention (antivirals)
- Host response mechanisms to identify targets for intervention (therapeutics)
- Host immune response to identify correlates of survival and protection (vaccines)
- Pathogen-reservoir interactions to identify mechanisms of transmission (prevention)

Dr. Feldmann provided a list of RML projects that already are under way or that will begin soon.

B. Presentation by Dr. Buchmeier

Dr. Buchmeier discussed the biosafety and biosecurity risks of research using Risk Group (RG) 4 (RG4) Mononegavirales cDNA and noted that the RAC's Biosafety Working Group (BWG) (a subcommittee of the RAC) had met several times to consider the related issues. He reviewed the RAC discussion at the March 3-4, 2009, RAC meeting regarding cloning full-length Ebola cDNA into *Escherichia coli* (*E. coli*) and pointed to the relevant section of the *NIH Guidelines* (regarding minor actions) that allows the RAC and the OBA to act on this request by the RML to extend the RAC's recommendation on full-length Ebola cDNA to include full-length Mononegavirales cDNA.

Dr. Feldmann has proposed to work with RG4 Mononegavirales (Marburg, Nipah, and Hendra viruses) such that plasmids carrying the full-length genomes of nonsegmented, negative-stranded ribonucleic acid (RNA) RG4 Mononegavirales for amplification in prokaryotes such as *E. coli* will be handled in "restricted" BL2 with limited and controlled access and under specific standard operating procedures. RG4 Mononegavirales are single-stranded, negative-sense RNA viruses, and no deoxyribonucleic acid (DNA) is produced during viral replication. The viral RNA genome and its cDNA copy are not inherently infectious in either mammalian or prokaryotic cells; additional functional viral proteins are required for replication or rescue in mammalian cells, and rescue is not possible in prokaryotes. Neither the RNA genome nor its derived full-length cDNA is considered to be a Select Agent.

Dr. Buchmeier reported that, at the RAC March 3-4, 2009, meeting, the BWG had made biosafety and biosecurity recommendations to the RAC regarding research involving DNA from RG4 Mononegavirales agents in nonpathogenic *E. coli*:

- *Biosafety*: Given the shared biological properties of these RG4 agents, the BSL recommended for cloning the full-length cDNA of Ebola into nonpathogenic *E. coli* also should apply to cDNA work with Marburg, Nipah, and Hendra viruses.
- *Biosecurity*: All research with these RG4 agents raises similar biosecurity concerns, and the RAC's assessment and recommendations for Ebola virus biosecurity should apply to all other RG4 viruses of the order Mononegavirales.

In addition, the BWG stated that lowering containment (to BL2) would be available only to PIs who plan to use the cDNA to rescue virus at BL4 or those with research agreements with another PI to rescue virus at BL4. The biosecurity risk of conducting this research at BL2 is undertaken to facilitate the ultimate goal of this research, which is to study the impact of manipulations to the genome on the full virus and facilitate the development of vaccines.

C. RAC Discussion

RAC members discussed the RML proposal and the BWG recommendations. Questions and comments included the following.

Dr. Buchmeier requested discussion about whether the RAC should be notified of a change in protocol or the establishment of a protocol, that is, how much monitoring of this program should be conducted externally and how much should be conducted by the institutional biosafety committee (IBC), with a periodic report from the IBC or the institutions. He was not concerned about RML *per se*, but potential future approvals might be more problematic. Dr. Buchmeier's concern centered on 5 or 10 years hence when procedures might erode as security becomes more lax. He suggested requiring at least an annual report to the OBA, which would not necessarily have to be reviewed by the RAC.

Ms. Shapiro asked what the laboratory workers know and whether the plans include them. Dr. Buchmeier responded that the RML must adhere to the U.S. Centers for Disease Control and Prevention standards for BL3 training—a specific, weeklong course with a curriculum that involves repetition and risk assessment, proper gowning and ungowning procedures, and other key skills and tactics. Dr. Feldmann explained the training procedures. Most of the people who will work with the full-length clone will be trained for high containment BL4, and most of the staff members are trained for the containment level in which they will work. All personnel who work in these facilities are fully aware of all the risks associated with the pathogens and are briefed on what happens if they are exposed.

In response to Dr. Ertl's query about training all workers to the BL4 training level, Dr. Feldmann explained that it takes up to 6 months for an individual to complete BL4 training, which would be too much effort for someone who will not work in that biocontainment. In addition, biocontainment training includes potential risks and exposures to that person, which are not justified if that person is not supposed to work in BL4.

Dr. Buchmeier stated the importance of establishing a procedure that would not be modified when the safety director or facility supervisor is replaced. The procedure should be adhered to specifically and the procedure should be reviewed periodically. In addition, if an accident occurs, the procedure should be reviewed and modified accordingly to avoid future accidents.

Dr. Feldmann explained that the RML will not have summer students or graduate students working in this restricted area; workers will be postdoctoral fellows who have experience in BL2 work and hopefully also in high-containment work and who will attend specific training and be informed about the risks. Despite the fact that the RML believes there is no risk in handling the plasmid, all workers will be trained and educated on the potential risk and will all be categorized in the same occupational health oversight protocol as anyone else going into high containment.

Dr. Federoff requested that the RML share its procedures with the RAC and the OBA so that other laboratories could benefit from the RML's experience. Dr. Feldmann and Dr. Hoe agreed to work together to redact RML procedures and provide them to the RAC and the OBA.

Regarding access to restricted areas by international visitors and other short-term guests, Dr. Feldmann confirmed that foreign visitors and students would not be working in the BL2 restricted area. Mr. Luke, Captain NIH police at RML, confirmed that all visitors must be escorted at all times and must be monitored any time they are in buildings where BL2 or higher containment research is being conducted.

Dr. Corrigan-Curay reiterated that guidelines for an annual report are already in place and that the expertise of IBCs should be respected. She requested that the RAC approve using the annual report format to the IBC, which includes information on changes made to the program during the past year; that report then could be shared with the OBA. The RAC expressed general agreement with this approach.

D. Public Comment

No public comments were offered.

E. Committee Motion 2

Although no official motion was made or seconded, Dr. Federoff asked that the RAC approve these two summarized recommendations:

- The RML should incorporate specific training and other procedures that are unique to the proposed research in restricted BL2 and should share those specific procedures on training and other procedures.
- An annual report regarding the restricted BL2 research should be given to the RML's IBC, including changes to the program based on experience; that report be shared with the OBA and the RAC.

The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

Dr. Corrigan-Curay will send a letter to the RML summarizing the decision including the two additional requests voted on by the RAC.

V. Day 1 Adjournment

Dr. Federoff, RAC Chair, adjourned Day 1 of the June 16-17, 2009, RAC meeting at 5:20 p.m. on June 16, 2009.

VI. Day 2 Call to Order and Opening Remarks

Dr. Federoff, RAC Chair, opened Day 2 of the June 16-17, 2009, RAC meeting at 8:20 a.m. on June 17, 2009.

VII. Minutes of the March 3-4, 2009, RAC Meeting

RAC Reviewers: Drs. Kanabrocki and Kirchhoff

Drs. Kanabrocki and Kirchhoff recommended acceptance of the March 3-4, 2009, minutes document, noting one substantive change that was needed: on page 33, change "BL3" to "BL2." Otherwise, the minutes document adequately reflected what transpired at the March 3-4, 2009, RAC meeting.

A. Committee Motion 3

Approval of the March 3-4, 2009, RAC meeting minutes was moved by Dr. Yankaskas and seconded by Dr. Federoff. The RAC voted unanimously by voice vote to approve the March 3-4, 2009, RAC meeting minutes.

VIII. Certificates of Appreciation for RAC Member Service to the NIH

Presenter: Lawrence A. Tabak, D.D.S., Ph.D., Director, NIDCR, NIH
RAC Members: Dr. Shah (*via teleconference*), Ms. Shapiro, and Dr. Somia

Dr. Tabak presented certificates to acknowledge the service and thank the three members who are rotating off the RAC after this meeting: Dr. Shah, Ms. Shapiro, and Dr. Somia.

IX. Discussion of Human Gene Transfer Protocol #0904-975: A Phase I Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Replication-Defective HIV-1 Vaccine (HIVAX™) in HIV-1 Infected Subjects Receiving Highly Active Antiretroviral Therapy

Principal Investigator: Margaret A. Fischl, M.D., University of Miami School of Medicine
Sponsor: GeneCure Biotechnologies LLC (Frank Tung, Ph.D.)
RAC Reviewers: Drs. Kahn, Somia, and Zaia

A. Protocol Summary

It is estimated that more than 50 million individuals worldwide will be infected with HIV type 1 (HIV-1) by the year 2010. In the United States and in other countries of the Western industrialized world, the development of highly active antiretroviral therapy (HAART) to treat HIV has led to substantial declines in morbidity and mortality. However, HAART is associated with high costs, poor compliance, significant toxicities, and the emergence of drug-resistant viruses. More importantly, more than 90 percent of HIV-infected individuals live in developing countries and have little or no access to antiretroviral therapies. The need is paramount for a safe and effective therapeutic vaccine to improve the immune control of viral replication and reduce the need for antiretroviral medications in HIV-infected individuals.

This Phase I study proposes to investigate the HIV-1 vaccine HIVAX™ at two increasing doses for people already infected with HIV. The primary objective of the study is to evaluate the safety of the vaccine; the study also will attempt to understand whether administration of the vaccine can increase immune responses directed at HIV and the effect of the vaccine on controlling the amount of HIV in the blood.

HIVAX™ is a replication-defective HIV-1 vaccine that is derived from an HIV attenuated by multideletions of the *pol*, *env*, *vif*, and *nef* genes. An envelope protein derived from vesicular stomatitis virus type G (VSV-G) is used to increase the transduction efficacy in immune cells. The safety and effectiveness of HIVAX™ were evaluated in animal studies, including monkey studies that used a simian counterpart of HIV (simian immunodeficiency virus [SIV]). HIVAX™ was found to be safe and to control SIV infection when monkeys were exposed to live SIV.

Thirty research participants, ages 18 to 60 years, will be enrolled in this study. Participants will be doing well on antiretroviral therapy, will have nondetectable amounts of HIV viral load in their blood, and will have recovered immune function as measured by CD4 cell count. The lower dose of the vaccine will be tested first, and if no side effects are seen, the higher dose then will be tested.

HIVAX™ will be administered as an injection at weeks 0, 8, and 16. Participants who receive the study vaccine during the vaccination phase will participate in a second phase of the study and will have

antiretroviral therapy interrupted for 12 weeks to assess the impact of the study vaccine on viral load. Evaluations and blood tests will be conducted to monitor the safety and possible effectiveness of the study vaccine.

B. Written Reviews by RAC Members

Thirteen RAC members voted for indepth review and public discussion of this protocol. Key issues included the need to address the possibility of recombination of the HIV-1 isolate (which is attenuated by multiple deletions) in humans who carry HIV-1 and the significant safety concern raised by the proposed interruption of HAART in patients whose infections are well controlled.

Three RAC members provided written reviews of this proposed Phase I trial.

Dr. Kahn focused his review on the informed consent document. He requested clarification of the point at which the blind would be broken, who will have access to the results of possible future blood tests on stored samples, and the conditions under which antiretroviral therapy would be restarted during the antiretroviral interruption phase. Dr. Kahn suggested that the “Benefits” section indicate that no benefits are likely to accrue as a result of participation in this trial and suggested the addition to the consent form of autopsy permission in case of death.

Regarding the preclinical data, Dr. Somia stated that the data would be more complete if the nonhuman primate study had recapitulated the clinical trial proposed in humans and asked whether additional studies could use a different SIV strain to study more than one strain; he also asked whether the investigators had conducted a biopsy after injection in monkeys or rats to evaluate the cell types that are transduced with the vaccine. Noting that the investigators had tested for and had not observed replication-competent lentivirus, Dr. Somia asked the investigators whether they had examined the possibility that the vector and helper recombine to restore any of the deletions introduced. He requested that the investigators provide more discussion about the value of the treatment-interruption phase of this study, particularly highlighting the possibility of creating drug-resistant strains in a patient group that is well controlled. Dr. Somia also requested that the investigators clarify several responses to *Appendix M* of the *NIH Guidelines*.

With regard to the study design, Dr. Zaia asked why the two proposed doses of vaccine had been chosen and whether lower doses had been considered, whether monitoring for mobilization of vector should occur, whether a 24-hour interruption of HAART would be sufficient given the serum half-life of tenofovir, and why the study does not propose to monitor for VSV-G antibody given that it is potentially an important factor in interpreting variations in vaccine responses. He requested an adjustment of the level at which the structured treatment interruption would cease (because of safety implications) and, regarding the exclusion criteria, asked the investigators to comment about potential enrollees’ access to influenza immunization and about the exclusion of potential enrollees who had received cancer chemotherapy. With regard to the *Appendix M* responses, Dr. Zaia queried as to the anticipated VSV-G immune response based on the vaccine studies in the monkey model. With regard to the informed consent document, he suggested that a procedure-trained witness be added to the informed consent process and that the risks of the structured treatment interruption and its potential effects on CD4 count be stated more clearly.

C. RAC Discussion

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

- Dr. Somia said it would be useful to know what cell types had been transduced with the injected vaccine; he suggested that it would be possible for the investigators to conduct such an experiment because there would be no complicating wildtype HIV sequences. The investigators agreed to conduct this experiment.

- Dr. Ertl expressed concern about the possibility that the three month interruption of HAART would have long term adverse effects on these fairly young research participants who were doing well at the time of enrollment. They will lose CD4 cells. Even if restarting HAART restores control at their preinterruption level, it is unknown whether this will have a long-term impact on life expectancy.
- Dr. Flint echoed other RAC members' suggestions to conduct an experiment using nonhuman primates under the same conditions proposed for the human trial, because of the persistence of many unresolved mechanistic and antigen-presentation issues.
- Ms. Shapiro reiterated the importance of including consent for autopsy in the informed consent document so that families might be more inclined to consent to autopsy if they knew that their deceased family member wanted autopsy to assist in learning something from their participation in this trial.
- Dr. Takefman asked whether the investigators plan to monitor, within the clinical trial, for presence of VSV-G DNA sequences in participant peripheral blood mononuclear cells (PBMCs) to make sure there is no transfer of envelope.

D. Investigator Response

1. Written Responses to RAC Reviews

The vaccine doses selected for this study are based on the preclinical study in rhesus monkeys. No side effects were observed in monkeys receiving up to 1×10^{10} transducing units per injection through subcutaneous and muscular routes for a total of 1×10^{11} transducing units. In the animal models, a minimum of 1×10^7 transducing units were needed in mice and 1×10^9 to 1×10^{10} transducing units were used in rhesus monkeys to elicit immune responses. Therefore, the current selected vaccine doses should be safe and should elicit immune responses in humans.

To study mobilization of the vaccine vector, the biodistribution study in mice demonstrated that vaccine virus was found only in lymph nodes and that it rapidly clears, with no detectable vaccine virus 3 days after injection.

The pause prior to vaccination (vaccine or placebo) is intended to cover a 24- to 36-hour period to accommodate longer acting antiretroviral drugs (such as tenofovir). Study vaccine/placebo will be given after a 36-hour interruption of a HAART regimen that includes tenofovir. The subcutaneous concentration of tenofovir should be at least tenfold lower than plasma concentration; therefore, a 36-hour pause is reasonable.

After discussion, the investigators decided that it is more appropriate to use restart antiviral agents based on the subject's on nadir HIV-1 RNA levels rather than an absolute single number. For safety reasons, combination antiretroviral therapy will be restarted for HIV-1 RNA greater than a 2.5-fold increase from a nadir (preantiretroviral treatment) on two consecutive measurements verified within 1 week.

Anti-VSV-G neutralizing antibodies were not found in rhesus monkeys vaccinated with HIVAX™. However, monitoring for VSV-G antibodies will be added to the protocol.

Based on current experience and the study population eligibility criteria (sustained HIV suppression and CD4 cell recovery to >500 cells/mm³ with a HAART regimen), it is anticipated that there will be limited risk for transient HIV viremia or negative impact on immunologic assays with a 2-week interval for flu vaccination prior to the screening visit. Therefore the protocol will be revised to allow for flu vaccination within 2 weeks of the screening visit.

The investigators stated that the nonhuman primate studies did not include HAART treatment and HAART interruption because completing antiretroviral treatment studies with nonhuman primates raised

several potential difficulties, including the stage of SIV infection in the monkeys (acute vs. chronic) and the effect of antiretroviral therapy on SIV viremia, which may not be as efficient with SIV compared with HIV. The outlined Rhesus monkey study was designed for safety. The investigators noted that they had demonstrated the efficacy of therapeutic vaccine in two persistent infected monkeys without HAART. It also was noted that HAART regimens may not be as efficient on SIV compared with HIV.

A biodistribution study in mice demonstrated that the vaccine virus was found only in lymph nodes and was not detectable in any major organ 3 days postinjection. Therefore, it is likely that the transduced cell types were dendritic cells.

HIVAX™ has normal function for integration. However, the majority of wildtype HIV-1 did not integrate in primary target cells, including CD4 cells and macrophages. Therefore, the investigators assume that the majority of HIVAX™ will not integrate into chromosomes yet will still elicit strong immune responses.

2. Responses to RAC Discussion Questions

With regard to including a request for autopsy in the informed consent document, Dr. Fischl noted that the risk of death from the vaccine in this patient population is very low, particularly since participants in this trial are already infected with HIV before given an experimental HIV therapeutic vaccine. She also noted that, regardless of the inclusion of a request for autopsy in the informed consent document, in the State of Florida, if the family denies an autopsy, then an autopsy is not conducted. However, Dr. Fischl stated that if a death occurs and the investigators do not know why it occurred, they will proceed with a request for an autopsy.

Dr. Fischl explained that the dose selected for this study was based on the animal studies in which a minimal biologic response dose was determined. Dr. Tung elaborated that the dose selection was based on studies using a mouse model as well as a nonhuman primate model. In the mouse model researchers demonstrated that the minimal dose required to elicit an immune response was 1×10^7 ; in nonhuman primate studies, doses of up to 1×10^{10} do not cause toxicity.

Dr. Fischl stated that the investigators plan to draw viable PBMCs in large numbers throughout the study, particularly during the treatment-interruption phase.

Regarding residual antiviral drug remaining longer than expected in participants' systems, Dr. Fischl explained that this trial is designed to allow for treatment interruption—a “pause” before and after the vaccination—to be conducted in a wide range of times. This flexibility was designed specifically so that when participants are taking a course of a longer-acting agent, the appropriate “pause” before and after giving the vaccination remains possible.

Dr. Fischl explained that the data show that HIV patients who interrupt their treatment typically rebound to their viral-resistance nadir. A therapeutic HIV vaccine trial has been completed by the AIDS Clinical Trial Group (ACTG) using the Merck monovalent vaccine. The data from that trial, which also included a treatment-interruption phase, showed no AEs either in the placebo group or in the vaccinated group. The investigators in the currently proposed trial have already talked with the PI and statisticians from the ACTG trial and would be able to review the ACTG data for the purposes of a historical control for the current trial.

Regarding the possible longterm effects of treatment interruption, Dr. Fischl noted that some recent treatment-interruption studies have followed participants in longterm followup studies. Results show that the virus is suppressed and that the CD4 cell count returns to preinterruption values—the immune system recovers. Although the participant populations are small in these studies, no negative impacts have been detected on longterm outcome, although impact data are difficult to interpret because, even with treated HIV infection, slow disease progression does occur.

Dr. Fischl reiterated that the five placebo-arm participants would not participate in the treatment-interruption phase.

Drs. Fischl and Tung agreed to add to the clinical protocol monitoring for presence of VSV-G DNA sequences in participant PBMCs to make sure there is no transfer of envelope.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

- Many questions remain about the mechanism of action of this vaccine. In particular, preclinical data are lacking on the following:
 - Identification of the cells that are transduced by the vaccine virus
 - Persistence of the gene expression
 - Data on how the brief vector persistence (3 days) seen in the biodistribution studies will affect the potential immunogenic effect of the vaccine
 - Whether treatment interruption will increase replication of the wildtype HIV, leading to an immune reaction to wildtype virus that would be difficult to distinguish from a vaccine-induced immune response

To address these fundamental questions and develop data to support a clinical study, additional preclinical studies need to be conducted. Specifically, the study should be in nonhuman primates and should be designed to closely model the design of the clinical trial (i.e., the monkeys will be in a chronic phase of infection with SIV and will receive HAART therapy). Although it will not be possible to replicate the clinical situation completely (e.g., the HAART drugs may not be as potent against SIV), such a study should help elucidate the risks of the trial and whether they are balanced by potential efficacy. In particular, every effort should be made to determine whether any immune responses are due to protein expression by the vaccine virus or to preformed protein delivery. Such information will help determine whether an antiviral treatment pause and interruption are required for efficacy.

- The study hypothesis is that the virus will transduce antigen-presenting cells. However, insufficient data were presented to demonstrate that subcutaneous injection results in transduction of antigen-presenting cells. As such, to determine which cells the vaccine virus transduces, a new biodistribution study should be conducted using immunocytochemistry and polymerase chain reaction (PCR) on biopsies of the subcutaneous tissue isolated before the third day after vaccination.

Clinical/Trial Design Issues

- The placebo control arm is designed to provide a comparison of immunologic data between the treatment arm and the control arm. The 12-week treatment interruption is designed to determine whether vaccination alters the virologic set point compared with pretreatment viral loads. Data from other HIV vaccine trials that have used treatment interruptions should be reviewed and a statistical analysis performed to help gauge the impact of structured treatment interruption on the rebound of viral load and the restoration of CD4+ counts after reinitiation of HAART.

- Additional work is needed to develop a way to distinguish the vaccine's effects from replication of the wildtype HIV as a result of the treatment interruption around the time of vaccination. If such distinctions cannot be made, it will be difficult to attribute the immunologic data to the vaccine.
- The trial should include monitoring of VSV-G sequences in PBMCs at 3, 6, 9, and 12 months to determine whether the VSV-G coding sequence is transferred by the vector vaccine to transduced cells.
- To better understand the possible interactions between the wildtype HIV and the vaccine strain, studies should be conducted to determine whether recombination can occur between the two viruses and/or whether the vaccine sequence is mobilized to other cells by the wildtype HIV.
- Participants are to stop antiviral medications for 24 hours to 36 hours prior to vaccination to prevent the antiviral medications from interfering with administration of the vaccine HIV strain. Serum levels of antiviral agents should be measured during this initial treatment interruption to confirm that this period is sufficient to enable levels of antiviral agents to drop, especially for those agents with long serum half-lives such as tenofovir.
- If there is evidence of vector persistence in preclinical or clinical studies, then longterm followup of participants enrolled in the trial should be conducted. For additional information, please refer to the FDA's "Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events" (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm>).

Ethical/Legal/Social Issue

- As this trial is a human gene transfer as defined in Section III-C-1 of the *NIH Guidelines*, information on autopsy as required in Appendix M-III-B-2-c should be included in the informed consent document.

G. Committee Motion 4

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. No motion was made or seconded that the RAC approve these summarized recommendations, but a vote was taken. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

[Note: At this point in the RAC meeting, Dr. Yankaskas took over as Chair of the RAC meeting, as Dr. Federoff had a conflict of interest regarding the subsequent agenda item. Dr. Federoff left the meeting room.]

X. Discussion of Human Gene Transfer Protocol #0904-981: A Phase I/II Trial Assessing the Safety and Efficacy of Bilateral Intraputamenal and Intranigral Administration of CERE-120 AAV-2-Neurturin in Subjects with Idiopathic Parkinson's Disease

Principal Investigators: William J. Marks, Jr., M.D., University of California, San Francisco (UCSF) *(via teleconference)*, and Mark Stacy, M.D., Duke University
Other Presenters: Kathie Bishop, Ph.D., Ceregene, Inc. *(via teleconference)*; Nicholas M. Boulis, M.D., Emory University School of Medicine; Charles Davis, Ph.D., CSD Biostatistics Inc. *(via teleconference)*; Jeffrey H. Kordower, Ph.D., Rush University; Herbert Meltzer, M.D., Vanderbilt University *(via teleconference)*; C. Warren Olanow, M.D., Mount Sinai School of Medicine; and Joao Siffert, M.D., Ceregene, Inc.

Sponsor: Ceregene, Inc.
RAC Reviewers: Dr. Ertl, Ms. Shapiro, Dr. Wei, and Dr. Yankaskas
Ad hoc Reviewers: John D. Elsworth, Ph.D., Yale University School of Medicine, and
Thomas B. Freeman, M.D., University of South Florida

Drs. Bartlett and Federoff recused themselves from consideration of this protocol due to conflicts of interest.

A. Protocol Summary

Parkinson's disease (PD) is a brain disorder that affects approximately 1 million people in North America. The most common symptoms of PD are trembling, muscle stiffness, slowed movement, difficulty walking, and poor balance and coordination. PD is a progressive disorder that also can cause other problems, including memory and sleeping difficulties.

Although its etiology is unknown, the pathogenesis of PD involves the progressive loss of function and eventual death of dopaminergic neurons in the substantia nigra (SN) that project to basal ganglia structures, in particular the striatal regions including the putamen. The dopamine precursor levodopa (L-Dopa) is the standard therapy for PD and acts by enhancing dopaminergic function of the degenerating nigrostriatal neurons. Although L-Dopa offers palliative treatment for PD symptoms, it does not retard progression of the disease. Moreover, the effectiveness of L-Dopa gradually declines, narrowing the therapeutic index and leading to the emergence of motor fluctuations ranging from "off" periods of bradykinesia/akinesia to drug-induced dyskinesias, both of which can be very disabling.

Neurturin (NTN) is a naturally occurring neurotrophic factor that has been shown in numerous animal studies to enhance the function and vitality of nigrostriatal dopamine neurons. Gene transfer of NTN cDNA allows for the continuous, controlled supply of NTN in and near the degenerating nigrostriatal neurons following a single neurosurgical procedure. Targeted delivery of NTN to nigrostriatal neurons using an AAV-2-based vector has potential as a safe and effective treatment for PD.

CERE-120 is an AAV-2-based vector encoding NTN shown to effectively deliver neurotrophic factor to the nigrostriatal system and protect nigral dopaminergic neurons from degeneration in both rodent and nonhuman primate models of PD. In addition, extensive rodent and nonhuman primate safety and toxicity studies have shown that administration of high doses of CERE-120 to the striatum is safe and well tolerated.

CERE-120 has been used in two PD studies. The first human study involved 12 PD patients; the goal of that study was to ascertain whether CERE-120 could be administered safely to humans. All 12 research participants in that study received CERE-120 injected into the putamen area of the brain, which connects to the SN and is also involved in controlling movement. To inject CERE-120 into the putamen, study participants underwent a surgical procedure; the results of this study showed that CERE-120 could be given safely.

In addition to looking at the safety of CERE-120, the second human study, which involved 58 PD patients, was designed to ascertain whether CERE-120 could improve the symptoms of PD. Thirty-eight participants received CERE-120 injected into the putamen, and 20 participants in a control group did not receive CERE-120 but underwent a sham surgery so that neither the participants nor the doctors treating them knew who had received CERE-120. When this study was completed in November 2008, the improvement in PD symptoms was no different for the research participants who received CERE-120 compared with those who received the sham surgery. Although some additional tests conducted during the study showed that CERE-120 might ameliorate PD symptoms slightly, the benefit was too small to continue testing CERE-120 in the same way used in both human studies.

Ceregene, Inc., is proposing a modified dosing paradigm for the planned Phase I/II protocol that includes injecting a small dose of CERE-120 directly into the SN. The study also will utilize a higher dose of CERE-120 in the putamen. The combination of an injection directly into the SN, the location of the cell

bodies of the affected dopamine neurons, along with an increased dose to the putamen, where the terminal fields of these neurons are located, should allow for robust expression of NTN throughout the dopaminergic system and ensure that the degenerating neurons receive adequate trophic support. Phase II of the study will include approximately 52 participants who will be randomized to receive CERE-120 (at the highest safe dose identified during the Phase I portion of the study) or sham surgery in a double-blind fashion. The primary objective of Phase II of this study will be to evaluate the efficacy of the modified CERE-120 dosing paradigm. Safety and tolerability also will be assessed carefully during Phase II.

B. Written Reviews by RAC Members

Nine RAC members voted for indepth review and public discussion of the protocol. Key issues included the assumptions underlying the trial design, the safety of the trial design and the proposed doses, the scientific and ethical justifications for proceeding at this point in product development with a sham neurosurgical arm as the control, and whether the current informed consent document adequately informs potential participants of the results of the previous trials and the potential risks and benefits of this proposed trial.

Four RAC members and two *ad hoc* reviewers provided written reviews of this proposed Phase I/II trial.

To determine whether this new protocol will be responsive to the RAC's past concerns, Dr. Ertl requested that the investigators provide a point-by-point explanation of whether and how these concerns would be addressed. She also requested a summary of the benefits to the vector recipients compared with the placebo group in the prior Phase II trial and a list of the AEs in the treatment and placebo groups. Dr. Ertl asked for a more complete description of the experimental evidence that led investigators to conclude that their vector would show better efficacy if injected directly into the SN.

Regarding study design, Ms. Shapiro asked the investigators to comment further on the justification for the sham surgery control group in this study (especially in light of the lack of demonstrated efficacy of CERE-120 in the prior trial), the risk-benefit balance, alternative research designs that would pose lower risks of harm to participants, and whether this design is scientifically valid for determining placebo effect. Regarding safety concerns, she reminded the investigators that the RAC's review of the initial CERE-120 trial included concerns about the potential adverse effects of NTN in nontarget areas. Given the mild and moderate AEs in the previous Phase II trial, along with two participant deaths that were determined to be unrelated to the study, Ms. Shapiro requested comment on safety concerns as well as on stopping criteria and other procedures that would be used by the DSMB. Regarding the informed consent documents, Ms. Shapiro requested clarification of several instances in which descriptions were confusing or vague.

With regard to the study design, Dr. Wei asked whether enough time is planned to allow for monitoring of the success or failure of the "treatment," whether an adaptive design (e.g., sample-size adjustment) might be preferable, and the risks to participants if the study does not result in at least some level of treatment benefit for PD. Regarding data analysis, he asked whether the investigators plan repeated measures and suggested that performing repeated measurement analysis might provide more powerful data than performing an analysis at only one time point. Dr. Wei also asked the investigators to provide the results of the data analysis from the previous CERE-120 Phase II trial and requested comment on how the knowledge gained from that trial had informed the design of this proposed trial.

Dr. Yankaskas asked the investigators to explain how the effects of intraputamenal and intranigral injections would be distinguished from each other and how the effects of the increased intraputamenal dose and the effects of the new intranigral injections would be distinguished. Since it has been demonstrated that retrograde axonal transport is reduced in moderate to advanced PD, he wondered whether anteretrograde axonal transport would be similarly affected and how responses to the proposed intranigral injections might be affected. In addition, Dr. Yankaskas requested that the investigators list the AEs observed in their prior studies of CERE-120 and that they comment as to whether any of those AEs are likely to be related to the vector. Compared with the prior study, the current study proposes an

increase experimental dose. Therefore, if AEs are related to the vector, then those AEs might increase in this trial because of the proposed increase dose compared with the prior trial.

Noting that the evidence for a deficiency in neuronal transport in PD is not strong, *ad hoc* reviewer Dr. Elsworth asked the investigators to comment on whether the proposed transport deficit is thought to be specific to NTN or to be a generalized deficit in transport and how much additional spread of NTN might be expected by raising the dose of CERE-120 injected into the striatum. With regard to the preclinical studies, he asked whether striatal dopamine levels had been measured in the rat or monkey studies to understand the implication of the decrease in tyrosine hydroxylase immunostaining. Dr. Elsworth asked whether the investigators had considered that CERE-120 would have a greater effect on the protection of surviving nigrostriatal dopamine neurons or on the restoration of lost striatal dopaminergic function and how long after CERE-120 administration an observation of a positive clinical effect might be expected. He asked whether, in the prior clinical trials, any participants had exhibited neutralizing antibodies to AAV-2 and whether the presence of those antibodies might affect the response in this study to intracerebral CERE-120. Dr. Elsworth also wondered whether injections of CERE-120 adjacent to but not into the SN would be sufficient and would be less damaging to the region.

Ad hoc reviewer Dr. Freeman stated that the following issues or concerns should be included in the informed consent document: the possibility of subdural hematomas, the expected postoperative course of the double-simultaneous deep brain stimulation (DBS) into the subthalamic nucleus (STN), how the crossover from the placebo arm into the therapeutic arm would be financed and when the crossover would occur if the results of this study show benefit, and why five positron emission tomography (PET) scans are necessary and the risks associated with PET scans. With regard to the clinical trial design, he noted the following issues for discussion: how the dose was chosen for the SN injection, whether the proposed novel method of injecting into the SN will have been tested adequately for safety with only six participants in the Phase I segment, why intranigral injections with CERE-120 would be expected to improve benefit, why participants should be exposed to the risk of a putamen injection, what management plans are in place to deal with the potential underpowering of this study, what caused the significant placebo effect in the prior Phase II trial, and how delayed AEs occurring in the Phase I segment of this trial will be managed with regard to the Phase II segment.

With regard to the placebo-controlled design of this proposed trial, Dr. Freeman noted these issues for discussion: how it will be possible to perform a placebo-controlled trial without obvious unmasking given the potential for altered mental status for as many as 5 days after DBS, how the blind will be maintained at the multiple study sites that may not have experience with maintaining a double blind within the operating room, and when and how the participants will be unblinded. With regard to the surgical methods of this proposed trial, he noted these issues for discussion: how the procedure will be standardized among the study sites and how the numerous surgeons will be trained, the rationale for a single injection and only two needle tracts in the putamen, and whether burr hole covers will be used on all participants even though their use is necessary only in the active arm of the trial. With regard to the volumetric and dosing issues of this proposed trial, Dr. Freeman noted these issues for discussion: why this protocol does not include more needle tracts and/or a significantly higher dose of the active agent for the putamen given the results of the monkey study, whether an adequate dose-escalation trial in humans should be performed before moving to a placebo-controlled trial, whether the human striatum can be reasonably influenced by this technique given the results of the rat study, what has been learned from the autopsy study related to the injections in the putamen, and the potential for off-time dyskinesias and the surgical and medical options for treating them in the setting of an irreversible therapy.

C. RAC Discussion

During the meeting, the following additional concerns were raised:

- Ms. Shapiro requested that the investigators add to the informed consent document discussion about who is sponsoring this study and information about the relationship of the PIs to the sponsor.

- Ms. Shapiro requested that the investigators add to the informed consent document language from *Appendix M* regarding request for autopsy.
- Dr. Wei asked for an explanation of the randomization schema proposed for the current trial.
- Dr. Ertl and Dr. Wei requested discussion as to whether the length of the trial (currently proposed at 15 months) is appropriate.
- Dr. Somia asked whether safety profiles had been conducted in both brain locations in monkeys.
- Dr. Yankaskas asked whether six participants is enough for the Phase I segment of this proposed trial before continuing forward to the randomized Phase II portion.

D. Investigator Responses

1. Written Responses to RAC Reviews

Regarding neuronal transport of NTN, the volume of NTN expression in the two autopsy cases is conservatively estimated to be approximately 15 percent. However, there was neither clear evidence of NTN staining in the SN nor evidence of an increased tyrosine hydroxylase (TH) response to NTN in the SN and only a very weak TH induction in the putamen. The investigators hypothesize that differences between what is observed in the advanced PD brain vs. animal models are most likely due to deficient axonal transport, as it is commonly recognized that retrograde transport is the means by which biological responses to vector delivery and protein expressed in the terminal field (e.g., striatum) are manifested in the neuronal cell body (e.g., SN). Moreover, impairment of axonal transport most often precedes dying back of axon terminals in multiple animal models and systems, with accumulating evidence that disruptions in axonal transport generally occur well in advance of cell death in many neurodegenerative diseases. The investigators noted that they did not believe that the degree of nigrostriatal neuron loss was so great in the postmortem specimens that the level of NTN expressed in the SN was too low to detect, as SN neurons were clearly visible in the autopsy cases.

Based on dose-response studies in rats and monkeys, it was estimated that a fourfold increase in CERE-120 to the human putamen should increase the volume of NTN expression in the putamen by as much as two times.

NTN has been shown to exert both neuroprotective and neurorestorative effects. Clinical studies of CERE-120 have been designed with the primary goal to detect a functional improvement over time. However, given the strong nonclinical evidence of neuroprotective and neurorestorative effects of neurotrophic factors in general and NTN in particular, it is expected that CERE-120 administration will both protect nigrostriatal neurons from ongoing injury and restore and improve the function of injured neurons in patients with PD. However, the study is designed to test only whether CERE-120 will confer a symptomatic improvement.

To date, 50 participants have received CERE-120. Serum testing for immunoglobulin G (IgG) antibodies was negative for NTN. Quantitative PCR for CERE-120 in serum was also consistently negative. Modest elevations in serum IgG antibodies to AAV were observed in some research participants who received CERE-120 (10 of 38 participants in Phase II) and in no participants who underwent sham surgery. There were no associated clinical or neuroimaging manifestations in any participant. Neither recruitment nor amplification of anti-AAV-2 antibodies had any impact on the safety, expression, or bioactive effects of CERE-120 or NTN in any animal study. Similarly, no AEs related to increased AAV-2 IgG antibody levels were observed in individuals who participated in the CERE-120 clinical trials.

Overall, the nature and incidence of AEs reported in the Phase II study, as well as in the longterm followup of participants who received CERE-120 (Phase I and Phase II participants), are consistent with the patient population enrolled in the study and with the nature of the surgical procedures employed. Accordingly, the most common AEs were headache/head pain/postoperative pain and postoperative

nausea. There were no SAEs reported in the CERE-120 Phase I study during the first year of followup (the primary study end point specified in the protocol). The Phase I and Phase II participants have continued to be followed long term (36+ months and 18+ months, respectively). None of the SAEs reported for participants undergoing sham surgery were deemed related to the surgical procedure, thus reinforcing the existing body of evidence that the sham surgery procedure employed in the Phase II study carries a low risk. The SAEs were carefully reviewed prospectively by Ceregene and by the independent Data Monitoring Committee (DMC) and were submitted to the FDA according to safety reporting requirements.

A comprehensive set of standard assessments of PD symptoms (including motor and nonmotor manifestations), health-related quality of life measures, cognition, and a variety of patient-reported outcomes were employed in both studies. A subset of participants also underwent fluorodopa PET scans. The efficacy data observed in the Phase I study have remained stable over time, with followup now at 36+ months. However, the small size of the study and the lack of a control group preclude a reliable interpretation of these data due to variability in the measures, potential bias in the assessments, and possible placebo effects. In the sham-surgery-controlled Phase II study, there was no difference in the primary outcome measure at 12 months, which measured a change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor manifestations) in the "off state" (off PD medications for approximately 12 hours). Several secondary measures at 12 months and other secondary analyses, conducted in a subset of participants (N=30) who were followed under double-blind conditions past 12 months (per protocol), suggest modest beneficial effects of CERE-120 that appear to increase over time. In particular, a statistically significant difference in UPDRS Part III (motor) in the "off state" (primary efficacy measure) favoring CERE-120 was seen at 18 months. Combined, these data suggest that CERE-120 confers a modest benefit to PD patients, but the magnitude of the effects are still below what experts would consider clinically meaningful and commensurate with the potential risks of this neurosurgical intervention.

Potential safety concerns associated with bilateral administration of CERE-120 to the SN were carefully considered. These concerns can be divided into potential neurosurgical risks (burr hole and needle penetration of the brain) and potential risks associated with NTN expression in the SN. Insertion of electrodes for bilateral DBS of the STN, a structure adjacent to the SN, and associated microelectrode placement for recording of the SN pars reticulata, are widely performed and can function as surrogates for the comparable surgical procedures proposed in this protocol. DBS of the STN has an overall low risk of complications, but it has occasionally been associated with transient postoperative delirium. Two recent large-scale studies of DBS for PD reported a 4 percent to 10 percent incidence of confusion within the first 3 months postoperatively following bilateral DBS lead implantation. Stereotactic needle placement that targets the SN and adjacent structures appears safe and will likely have similar risks to other widely utilized procedures. These risks are clearly explained in the informed consent document.

If CERE-120 is found to be efficacious and safe after completion of the blinded portion of the Phase II study, participants who have undergone sham surgery as part of a previous CERE-120 trial will be eligible for CERE-120 administration provided they have no medical or surgical contraindications. Ceregene will pay the costs related to CERE-120 administration and safety followup.

Potential crossover, open-label CERE-120 administration will be performed as part of a separate clinical trial that will be initiated following a complete analysis of the Phase II study results by the sponsor and careful, independent review of the data. Eligible participants will be provided with a separate informed consent document specifically for the new study. The timing of potential crossover surgeries, which could begin approximately 3 years after the first research participant is enrolled in the Phase II portion of this study, will be clarified in the informed consent document.

Placebo effect is increasingly a concern in double-blind, placebo-controlled studies, particularly in PD trials. Although it is difficult to neutralize placebo response completely, increasing effort will be made to reduce participant, family, and investigative team expectations during the investigator initiation meeting and throughout the study.

Regarding training at multiple sites, the sites selected for this study have participated in a previous Ceregene Phase II study, which was also double blind, randomized, and sham-surgery controlled. This proposed study will be the third study conducted by Ceregene employing a sham-surgery controlled group. Ceregene has successfully developed and implemented a comprehensive training program for all personnel involved in such studies. General anesthesia will be employed to ensure blinding during the surgical procedures. Strict blinding safeguards have been implemented successfully in previous trials, including the concealing of operating room windows, careful selection of staff members participating in the surgical procedure, and scripted interactions between the surgeon and participants, family members, and the blinded study team.

The DMC will be composed of at least one experienced neurologist familiar with neurosurgical procedures, one experienced neurosurgeon, one neuroradiologist, and one statistician. Unblinded reviews of all safety data from this study will be conducted regularly by the DMC. In addition, the DMC will have real-time access to the entire safety database. If any clinical concerns arise related to CERE-120 administration, a determination will be made by the DMC as to whether to halt study enrollment. No prespecified stopping rules will be set in place given that the DMC members will be highly experienced.

To eliminate a potential confound in the assessment of the safety and efficacy of CERE-120, the investigators will request that participants not undergo DBS for at least 1 year after receiving CERE-120 if they participate in the Phase I portion of the study. Phase II participants will be requested to refrain from DBS until after the completion of the double-blind followup period. This means that each Phase II participant will be requested not to undergo DBS for a time period lasting from 15 to 24 months after study surgery, depending on when the participant enrolls in the study. Although the investigators prefer that participants refrain from undergoing DBS after the study surgery for sufficient time to allow reasonable assessment of the effects of CERE-120, the study protocol will not prohibit participants from undergoing DBS if it is in their best medical interest to do so. Participants who have undergone surgery in the study may opt to receive DBS at any time after surgery and still be followed until study completion. The informed consent document will be modified to clarify this option.

In response to Dr. Yankaskas' questions, the investigators noted that they did not believe it is necessary (or readily feasible) to clinically differentiate the effects of NTN expression in the SN vs. the putamen.

The sample size estimation was refined to reflect additional discussions with the statistician and actual data obtained from the recently completed CERE-120 Phase II study (e.g., standard deviation). The current sample size estimation is as described below:

“The primary endpoint is the change from baseline in the MDS-UPDRS Part III: Motor score in the practically defined ‘off’ condition. Assuming a standard deviation of 10 and the use of a two-sided, two-sample t-test at the 5 percent level of significance, a total sample size of 52 participants (26 in the CERE-120 group; 26 in the sham-surgery controlled group) is required in order to have at least 90 percent power to detect a difference between treatment groups of 9 points.”

2. Responses to RAC Discussion Questions

Dr. Kordower stated that he recently completed *post mortem* analysis of 29 Parkinson's brains between 1 and 27 years postdiagnosis. All of them had remaining TH-containing fibers to varying degrees within the putamen, so substrate remains—although it is diminished—for retrograde transport. In a *post mortem* sample analysis, there was an average of 50-percent loss of neural melanin-containing cells, also resulting in enough substrate left on which trophic factors could work. TH staining in those same samples show about an 80-percent loss. These analyses indicate that cells are available and viable for trophic factor stimulation in the Parkinsonian brain all the way up to *post mortem* evaluation. Therefore, the investigators believe that enhancing the delivery of NTN to the striatum will utilize the breadth of fibers that remain and will allow activation of the numerous cells that are melanin containing, clearly nigral striatal, and viable in the Parkinsonian nigra that have lost phenotype due to the general disease process.

Regarding direct injection into the SN, Dr. Siffert explained that the investigators believe that injecting directly in the area where NTN should be expressed is the most objective means to get the biologic effect that this trial is attempting to accomplish. The risk of injecting into the SN has been reviewed extensively with the investigators' surgical colleagues and with others around the world; this injection has been deemed to be a safe neurosurgical procedure based on the fact that this procedure is conducted routinely in DBS surgeries. The investigators reported no toxicity of CERE-120 injection at any dose, in any of the animal models as well as none being seen in the two autopsy cases. The risks are minimal, and injection directly into the target site is the most advisable way to proceed.

Dr. Boulis corroborated the lack of significant difference in AEs between the sham group and the injection group, which substantiates that the side effects seen in the prior trial were the result of anesthesia, not of penetration of NTN or CERE-120.

Dr. Kordower described a study in which the investigators directly injected the SN and upregulation of TH and other dopaminergic markers was observed. One or two animals in that study did demonstrate spread into the ventral tegmental area, but there was no obvious behavioral change in those animals relative to animals in which expression was circumscribed within the SN. A slight increase in TH was observed in the lateral septum but not observed in the cortex in those animals, but no changes in the general health of the animals were observed—the animals were indistinguishable from animals in which the midbrain injection was completely localized to the SN.

Dr. Siffert agreed to add to the informed consent documents information about the sponsorship of this trial. The wording will make it clearer that this trial is being sponsored and paid for by Ceregene. The investigators are reimbursed for the clinical trial costs, and this contract is negotiated directly with their institutions; reimbursement is not a direct payment to the investigators but is paid through the fees applicable to clinical trials.

Dr. Siffert agreed that sham surgery is not an innocuous procedure, which is why so much consideration goes into the trial design, safeguards, and clinical protection of the participants in this trial. However, the investigators believe that the magnitude and frequency of the AEs have been such that research participants tolerate them. None of the individuals who underwent the sham surgery procedures in the prior trial had what were considered SAEs that were deemed related to the surgery, and all continued on with their lives without lasting consequences of the transient AEs they experienced.

In defense of the need for including a sham-surgery controlled group, Dr. Siffert reiterated that the investigators believe there is no reliable way to measure the efficacy of an intervention such as the one proposed unless the trial includes a control group that is blinded to the experimental treatment. A double-blind, well-controlled sham surgery procedure remains the "gold standard" by which to test the efficacy of the proposed drug and is a warranted approach.

Regarding the randomization schema for the proposed trial, Dr. Siffert explained that the currently proposed one-to-one randomization is statistically efficient in that fewer participants will be exposed to the experimental drug for the same amount of statistical power. The prior study used a randomization schema of two-to-one; the reasoning was that the two-to-one randomization was thought to be more palatable in terms of chances of receiving the experimental treatment.

Dr. Siffert reiterated that the minimal followup for the proposed study is 15 months. The investigators expect that enrollment will take approximately 1 year, so by the time the last participant completes the study, participants who enrolled early in the study could be blinded for as long as 27 months provided they remained in the study. Therefore, followup times will range from 15 months to as long as 27 months in at least some participants, which will result in blinded data prospectively collected that can be compared on both treatment arms.

With regard to whether safety profiles have been conducted in both brain locations in monkeys, Dr. Siffert responded in the affirmative and noted that toxicity had never been observed. The maximal tolerable dose (MTD) is merely a practical MTD as no MTD had been reached.

Dr. Siffert clarified the issues surrounding the timing of the first six participants in the Phase I proposed trial. He noted that, in the prior trial, the vast majority of the AEs occurred within several days of the surgery. Longterm followup showed that few AEs emerged later, and very few were SAEs, most of which were expected in individuals with PD. Before the Phase II segment begins, there will be a range from 3 months follow-up for the last participant and 9 months for the first participant in Phase I. The observations from clinical data of 50 research participants show that the bulk of the AEs occur early. There have been no delayed AEs detected, even with the administration of CERE-120 followed up to 4 years in some individuals. In addition, monkey studies with 30 times more viral genomes and a followup period of 12 months showed no toxicities—5 of those monkeys received injections into the SN—and every animal that was ever treated had robust NTN expression in the SN.

E. Public Comment

Wilson DeCamp, Ph.D., who is retired from the FDA, is a PD patient, and is a member of the Parkinson Pipeline Project, spoke of concerns about the placebo effect, sham surgery and the need for improved trial designs. He encouraged the RAC and Ceregene, Inc., to seek improved trial designs that include sham surgery and placebo controls. Dr. DeCamp implored the RAC to keep in mind that PD patients have insights that may help improve the focus of these trials. Although a primary end point of global impact is laudable, smaller changes such as the ability to get up during the night and go to the bathroom unassisted or the ability to get dressed alone are significant trial end points for many PD patients. Insisting on a trial design that requires a large behavioral change might result in keeping a therapy from the patients who would benefit from it.

Arnold Kuzmack, Ph.D., a retired environmental scientist at the U.S. Environmental Protection Agency and also a member of the Parkinson Pipeline Project, expressed concern about the placebo effect and suggested that the scientific community focus on issues related to the use of placebo. Particularly in PD, when individuals join a study in which they could possibly receive a new treatment and are being examined by doctors, their dopamine levels are affected—which is one of the reasons that PD studies may find it particularly difficult to use placebo controls.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issue

- Autopsy data from two participants in Protocol #0607-788 failed to show evidence of NTN protein in the SN, whereas animal data with putamen injection consistently showed NTN in the SN. One hypothesis is that the vector and/or the protein was not transported down the axon from the putamen to the cell bodies and that this was due to deficiencies in neuronal transport caused by the disease. However, PCR to detect the AAV-2 vector was not performed. The autopsy tissues should be reexamined to determine whether the AAV-2 vector was present in the SN and, if so, at what levels (i.e., compared with studies involving nonhuman primates). These data will inform as to whether direct injection of CERE-120 into the SN is likely to result in expression of NTN or whether there are other factors that could prevent AAV-2 from expressing NTN even if it reaches the SN.

Clinical/Trial Design Issues

- Given that Protocol #0607-788 failed to show efficacy and that most of the changes in the UPDRS scores were seen in the first few months after study participation, an adaptive design or other interim analysis should be considered. This would allow the clinical data obtained after the first few months to be analyzed prior to enrollment of all 52 participants. If this approach is not feasible, a discussion of why it is not feasible should be included in the protocol. In Protocol

#0607-788, differences between the study agent and placebo arm began to appear starting at 15 months. As such, it would make more sense to follow the efficacy end point longer, even up to 24 months, rather than the proposed 15 months.

- Given data indicating that only 15 percent of the putamen showed an increase in NTN expression in Protocol #0607-788, in addition to increasing the dose of the study agent in the Phase II portion of this study to optimize putamen distribution, it would be prudent to consult with a neurosurgeon to optimize a predetermined target to ventral, dorsal, rostral, and caudal coordinates with respect to a fixed landmark in the brain such as the anterior commissure. In addition, distribution of the vector and expression of NTN around the injected sites are critical. As such and given that there are other AAV serotypes that have better tropism for neurons, the protocol should justify the use of a vector based on serotype 2.
- A baseline and ongoing psychiatric evaluation of participants during the trial should be added to monitor for any adverse effects or benefits that may occur from NTN spreading outside the SN, for example, to the ventral tegmental area.
- Five percent to 10 percent of individuals who undergo double-simultaneous DBS into the STN experience prolonged confusion after surgery. Since this adverse effect would not be seen in the placebo group, the blinding mechanism should be reviewed to ensure that it can be maintained if such an event occurs.

Ethical/Social/Legal Issues

- The informed consent document should be modified as follows:
 - Make clear that although participants are being asked to defer DBS until after the trial and if they decide to get DBS they will no longer be followed for efficacy, they do have the option of getting DBS and continuing to be followed in the study for safety purposes
 - Since AEs related to the double-simultaneous DBS could result in a longer hospital stay, be less specific regarding the expected length of the hospital stay to preserve the blinding
 - Describe the relationship between the sponsor of the study, Ceregene, and the investigators, and any financial incentives provided to the investigators to participate in the trial
 - Inform participants, per *Appendix M-III-B-2-c* of the *NIH Guidelines*, that at the time of death, no matter what the cause, permission for an autopsy will be requested of their family and ask participants to advise their family of the request and of its scientific and medical importance

G. Committee Motion 5

Dr. Yankaskas summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved that the RAC approve these summarized recommendations. The vote was 11 in favor, 0 opposed, 0 abstentions, and 2 recusals.

[Note: At this point in the RAC meeting, Dr. Federoff returned to the meeting room and resumed his position as Chair of the RAC meeting.]

XI. Discussion of Human Gene Transfer Protocol #0904-976: A Phase I Ascending-Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent Glioblastoma Multiforme

Principal Investigator: Manish K. Aghi, M.D., Ph.D., UCSF
Sponsor: Tocagen Inc. (Douglas J. Jolly, Ph.D.)

Other Presenters: Dan Pertschuk, M.D., Tocagen Inc.
RAC Reviewers: Drs. Fan, Gerritz, and Williams

A. Protocol Summary

Glioblastoma multiforme (GBM) is the most common form of malignant brain tumor in adults, accounting for 50 percent to 60 percent of primary brain tumors. Despite major improvements in health care during the past decade, the average lifespan for patients diagnosed with GBM is still only 12 to 15 months. Hence, there is an unmet need to develop effective new approaches against this devastating disease. Gene delivery is one such approach; however, clinical trials of gene delivery products that involve the use of conventional, replication-defective vectors or cell-killing viral vectors that stimulate potent immune responses have resulted in disappointingly low and therapeutically inadequate infection and reduction of brain tumor cells.

Tocagen Inc. is proposing a clinical study with a new, replication-competent, gene-delivery viral vector that consists of a replication-competent mouse leukemia virus expressing the cytosine deaminase (CD) gene. The CD gene occurs naturally in yeast, fungus, and some bacteria, but not in humans or other animals, and functions biologically by converting the already-approved and widely used antifungal drug flucytosine to the cell-killing drug fluorouracil, which also is an approved and widely used anticancer drug. On the basis of studies obtained in mice, this viral vector preferentially infects brain cancer cells, which then act as a reservoir for the virus to multiply and spread to additional brain cancer cells. Within such studies, transduction has been shown to be restricted to actively dividing tumor cells without evidence of significant spread to extratumoral sites, resulting in prolonged survival without detectable systemic side effects. An important advantage of the therapeutic use of a murine leukemia virus (MLV)-based, replication-competent retroviral (RCR) vector includes inherent tumor selectivity, due to the inability of MLV to infect nondividing cells.

When the prodrug flucytosine is administered orally, some of the drug passes through the blood-brain barrier, and the virus-infected brain tumor cells containing the CD gene convert flucytosine to the cell-killing drug fluorouracil. In this manner, the brain tumor cells are destroyed, leaving the healthy brain cells intact. Although the viral vector containing the CD gene will be administered only once directly into the brain tumor, multiple rounds of the oral prodrug flucytosine will be given over time to allow any remaining active vector to infect whatever brain tumor cells remain after the previous prodrug treatment and to maximize the killing of all infected brain tumor cells over time.

The proposed clinical study will evaluate the safety and clinical effects of a single intratumoral injection of this vector to research participants with recurrent GBM for which there are no approved systemic treatments. Since the vector stably integrates into the tumor genome, multiple cycles of dosing with the approved oral prodrug flucytosine are proposed in the clinical study. The first protocol will evaluate single, increasing doses of the viral vector (referred to as Toca 511) when injected directly into the tumor using transcranial delivery. Participants will be patients with recurrent GBM who have previously received surgery, radiation therapy, and chemotherapy; neither radiation nor chemotherapy will be allowed during this study. After the initial injection, participants will wait 3 weeks while the vector spreads throughout the tumor, after which oral flucytosine will be administered daily for 1 week. This prodrug administration cycle (3 weeks off flucytosine, 1 week on) will be repeated until intolerance to the prodrug develops or the participant's tumor progresses.

Participants will undergo MRI scanning every 2 months after beginning dosing with flucytosine. Safety assessments will include flucytosine blood levels; monitoring blood and urine for virus, clinical chemistries, and hematology at selected time points; and recording any AEs. Efficacy assessments will include tumor response, progression-free survival at 6 months, and overall survival. All participants will be followed for 6 months. Those participants who appear to be benefiting from treatment may elect to roll into a continuation protocol that would allow them to continue treatment with flucytosine.

B. Written Reviews by RAC Members

Nine RAC members voted for indepth review and public discussion of this protocol. Key issues included the novelty of the RCR vector with amphotropic envelope and the rationale and risks and benefits for the use of this vector in this population.

Three RAC members provided written reviews of this proposed trial.

Dr. Fan expressed concern that GBM patient-participants might experience enhanced spread of Toca 511 to other cells or tissues because of immunosuppression due to prior chemotherapy or radiation, and if Toca 511 infection does spread to the bone marrow or other hematopoietic tissues, flucytosine treatment could lead to cell killing in these compartments. He asked whether this issue had been addressed in the animal studies, whether the investigators intend to monitor the vector's effects on hematopoiesis in research participants, and whether the investigators had considered modifying the Toca 511 long terminal repeats to favor expression in glioblastoma cells. Dr. Fan asked the investigators to comment on whether development of immune responses to the vector would be expected to limit the duration of the vector or the success of second injections. He asked about the possibility of recombination between the vectors and xenotropic MLV-related virus (XMRV), which has been detected in humans with prostate cancer. He also asked whether GBM cells had been tested for the expression of APOBEC3G, a factor shown to restrict MLV infection. Given the poor prognosis of recurrent GBM, it is likely that some research participants would die during the study due to underlying disease; Dr. Fan asked how these fatalities would be distinguished from deaths due to AEs.

Dr. Gerritz focused her written review on the informed consent document. She noted several instances of the use of "gene therapy" rather than "gene transfer"; discrepancies in several locations of the number of participants anticipated to be enrolled in this trial; and unexplained descriptors such as "likely," "less likely," and "rare but serious." Dr. Gerritz suggested that the investigators include information about the possible side effects that could accompany the use of Toca 511, since the potential side effects of injecting an experimental product into the brain and taking flucytosine by mouth are listed. Rather than leaving participation decisions to the investigators to determine what might change a participant's mind about entering into and continuing in this study, Dr. Gerritz suggested that the investigators include language indicating that they will inform participants if they become aware of any evidence of new risks or side effects, especially given that unforeseen results might occur.

Dr. Williams requested additional information about how the dose volume would be determined for each research participant and about the relationship between the volume of vector that can be tolerated via human brain injections and the minimal effective dose. He requested additional data regarding the toxicity, efficacy, and biodistribution of the proposed clinical vector and suggested that, at autopsy, all tumor cells be analyzed for vector insertion sites and drug-resistance profiles. Dr. Williams also suggested that the investigators include wording in the protocol and in the informed consent document to prohibit the use of immunosuppressive drugs following administration of the vector to help ensure that participants' immune systems remain intact to reduce the risk of the emergence or persistence of RCR retrovirus.

C. RAC Discussion

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

- Dr. Ertl discussed the importance of taking samples of PBMCs before and after dosing. She advised the investigators to take many PBMC samples before and after dosing because doing so would allow the investigators to figure out the linkage to efficacy before moving to additional clinical trials.
- Dr. Borrer requested several wording changes in the informed consent document, including fleshing out the discussion about how Toca 511 will be injected into the tumor, a description about the dose escalation that would include a discussion about the differences in risks as well as

differences in benefits in the different cohorts, overly promising statements about the certainty of results, and changing “the FDA requires followup” to “the FDA requires us to ask for followup.”

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators presented the preclinical studies of the toxicity, efficacy, and biodistribution of the vector in multiple adult animal studies. Preliminary evidence indicated efficacy (survival) with Toca 511 in both immunodeficient and immunocompetent mouse tumor models. The ongoing good laboratory practices (GLP) toxicology study was designed to detect any abnormalities (e.g., clinical signs, hematology, histopathology of all tissues) associated with the intracranial administration of the vector at three different doses, spanning a hundredfold range, with and without subsequent flucytosine administration in mice, which is the species also used in the efficacy studies.

It is possible that recurrent tumors could be resistant to or escape flucytosine treatment. If that occurs, the investigators agreed to analyze those tumors for parameters such as integration site clonality and flucytosine resistance.

Although immune suppression may enhance Toca 511 spread through the tumor and to other cells or tissues, published studies suggest that, in adults, the presence of even partial immune function is able to control spread of the virus and prevent subsequent development of disease. The investigators believe that the current protocol, with the addition of criteria to exclude participants with lymphopenia, will select participants with immune function that is adequate to control infection following intratumoral injection of MLV. They agreed with the suggestion to exclude participants with lymphopenia and that participants not receive immunosuppressive drugs, other than dexamethasone, following administration of the vector. The protocol also excludes patients with HIV and participants taking more than 8 mg of dexamethasone per day at entry.

In response to Dr. Fan’s question about potential hematological toxicity, the investigators noted that an arm in the ongoing GLP safety study is intended to look for hematologic toxicity. Preliminary hematology data from this study in immunocompetent mice treated with virus and flucytosine showed no difference from the controls. However, the toxic effects of flucytosine on hematopoiesis are well documented, and this possibility will be monitored closely in the proposed clinical trial.

Regarding the possibility of coinfection with XMRV, the investigators noted that XMRV has been reported to be found in only a small percentage (1.7 percent) of the general population, and it is unknown whether recombination with this virus would negatively impact the health of the adult host. However, all participants will be monitored carefully for persistence of replication-competent MLV, and those participants with persistent viremia will provide the opportunity to investigate and characterize any significant changes to viral sequences.

Dr. Kasahara has tested cells from four primary GBM tumor explants, including CD133+ cells, and has demonstrated infection using an RCR-GFP vector, although these cells were not tested for expression of APOBEC3. Other investigators have reported the presence of APOBEC3 in human brain cells and in U-87 tumor cells. Although APOBEC3 may interfere with infection, there is apparently sufficient infection with Toca 511 vector as evaluated in CT26 and U-87 cell lines to demonstrate efficacy. These data suggest that although APOBEC3 may partially restrict MLC infection, this inhibition is relative and can be overcome with an RCR MLV vector such as Toca 511.

The investigators agreed to make Dr. Gerritz’s suggested changes to the informed consent document.

2. Responses to RAC Discussion Questions

Given that deaths will occur during this study, Dr. Pertschuk noted that attribution of those deaths will be a challenge for the research team. According to RAC guidance, all research participants will be asked to

agree to an autopsy should they die during the study or thereafter, which would provide the most reliable evidence regarding the cause of death. Short of being able to conduct an autopsy, Tocagen's general study policy about attribution of research participant death is to analyze the timing of SAEs in relation to whether the tumor is responding or progressing; in addition, monitoring will take place for hematology, viremia, and any other kind of evidence of virus in the bloodstream. If the tumor is growing larger, that is the most likely cause of death. Death is considered an outcome and not an event, so there must be an event that causes the fatality. As the PI, Dr. Aghi's conclusion as to causality or relationship to the study drug or study treatment is final and cannot be overridden by the sponsor.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Clinical/Trial Design Issues

- To facilitate studies of the role of the immune response in efficacy and any unexpected AEs, PBMCs are to be collected before and after vector administration.
- If possible, *post mortem* analyses of tumor cells should be carried out to identify vector insertion sites and drug-resistance profiles. Such studies would advance understanding of the mechanisms at work. In addition, levels of human APOBEC3G (hA3G), a cellular factor that restricts replication of retroviruses, should be examined in the cells because high levels of hA3G may interfere with the vector's replication.
- The human RCR XMRV has been detected in humans with prostate cancer. Data regarding the prevalence and significance of XMRV are limited at this time. However, as additional prevalence data become available, it may become important to consider XMRV status, as determined by serology or other appropriate techniques, as an exclusion criterion to avoid recombination between XMRV and Toca 511 in infected individuals.

Ethical/Social/Legal Issues

- Although efforts have been made in response to initial RAC review comments to eliminate misleading language from the informed consent document, more editing is necessary to eliminate presumptions of efficacy and statements about the potential scientific contributions of the study. This is particularly important because of the study design, a Phase I trial, and the study population (i.e., potentially vulnerable participants who lack therapeutic options).
- The informed consent document should clearly explain why participants are asked to participate in longterm followup studies and that they are free to participate or not and free to withdraw at any time if they do choose to participate.
- The informed consent document should include information regarding the SAEs that occurred in gene transfer trials for X-linked severe combined immunodeficiency and the risks of insertional mutagenesis caused by retroviral vectors in CD34+ cells. Even though this protocol involves a different type of cell population and organ system, participants in any study using a retroviral vector should be informed of the previous AEs.

G. Committee Motion 6

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Although no official motion was made or seconded, Dr. Federoff asked that the RAC approve these summarized recommendations. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

XII. Closing Remarks and Adjournment

Dr. Federoff thanked the RAC members and the OBA staff and adjourned the meeting at 3:00 p.m. on June 17, 2009.

[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.]

Jacqueline Corrigan-Curay, J.D., M.D.
RAC Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and the following 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.
Executive Vice President and Executive Dean
Georgetown University Medical Center
Building D, Room 120
4000 Reservoir Road, NW
Washington, DC 20007

Members

BARTLETT, Jeffrey S., Ph.D.
Principal Investigator
Center for Gene Therapy
The Research Institute
Nationwide Children's Hospital
Associate Professor of Pediatrics and of
Molecular Virology, Immunology, and Medical
Genetics
College of Medicine
The Ohio State University
Room WA3016
700 Children's Drive
Columbus, OH 43205

BUCHMEIER, Michael J., Ph.D., M.S.
Professor
Departments of Molecular Biology and
Biochemistry
Division of Infectious Disease
Department of Medicine
School of Medicine
University of California, Irvine
McGaugh Hall, Room 3205
Irvine, CA 92697

ERTL, Hildegund C.J., M.D.
Director
Vaccine Center
The Wistar Institute
School of Medicine
University of Pennsylvania
3601 Spruce Street
Philadelphia, PA 19104

FAN, Hung Y., Ph.D.
Director
Cancer Research Institute
University of California, Irvine
Sprague Hall, Room 106
Mail Code 3905
Irvine, CA 92697

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

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

KANABROCKI, Joseph A., Ph.D.
Assistant Dean for Biosafety
Associate Professor of Microbiology
Department of Microbiology
Biological Sciences Division
The University of Chicago
Cummings Life Science Center, Room 117
920 East 58th Street
Chicago, IL 60637

KIRCHHOFF, Louis V., M.D., M.P.H.
Professor
Departments of Internal Medicine (Infectious
Diseases) and Epidemiology
Roy J. and Lucille A. Carver College of Medicine
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

ROIZMAN, Bernard, Sc.D.
Joseph Regenstein Distinguished Service
Professor
Departments of Microbiology and of Molecular
Genetics and Cell Biology
Biological Sciences Division
The University of Chicago
910 East 58th Street
Chicago, IL 60637

SHAH, Prediman K., M.D.
Director
Division of Cardiology
Atherosclerosis Research Center
Cedars-Sinai Medical Center
Suite 5531
8700 Beverly Boulevard
Los Angeles, CA 90048

SHAPIRO, Robyn S., J.D.
Partner
Drinker, Biddle and Reath
Suite 2000
777 East Wisconsin Avenue
Milwaukee, WI 53202

SOMIA, Nikunj V., Ph.D.
Associate 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
School of Medicine
University of Maryland
Suite 500
16 South Eutaw Street
Baltimore, MD 21201

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

WILLIAMS, David A., M.D.
Chief
Division of Hematology/Oncology
Director of Translational Research
Children's Hospital Boston
Leland Fikes Professor of Pediatrics
Department of Pediatrics
Harvard Medical School
Karp Family Research Building, Room 07212.0
300 Longwood Avenue
Boston, MA 02115

YANKASKAS, James R., M.D., M.S.
Professor of Medicine
Division of Pulmonary and Critical Care
Medicine
Department of Medicine
School of Medicine
The University of North Carolina at Chapel Hill
Thurston Bowles Building, Room 7011
Chapel Hill, NC 27599

ZAIA, John A., M.D.
Professor and Chairman
Division of Virology
Beckman Research Institute
City of Hope
1500 East Duarte Road
Duarte, CA 91010

***Acting Director, OBA
RAC Executive Secretary***

CORRIGAN-CURAY, Jacqueline, M.D., J.D.
Executive Secretary
Recombinant DNA Advisory Committee
Acting Director
Office of Biotechnology Activities
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

Acting Director, Office of Science Policy

PATTERSON, Amy P., M.D.
Acting Director
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

Ad Hoc Reviewers and Speakers

ARMINIO, Thomas, R.N., M.P.H. (*via teleconference*)
Biosafety Manager
Occupational Health
Rocky Mountain Laboratory
National Institute of Allergy and Infectious Diseases
National Institutes of Health
903 South 4th Street
Hamilton, MT 59840

BLOOM, Marshall, M.D. (*via teleconference*)
Associate Director
Division of Intramural Research
Rocky Mountain Laboratories
National Institute of Allergy and Infectious Diseases
National Institutes of Health
903 South 4th Street
Hamilton, MT 59840

CLAYTON, Ellen Wright, M.D., J.D. (*via teleconference*)
Rosalind E. Franklin Professor of Genetics and Health Policy
Professor of Pediatrics
Professor of Law
Director, Center for Biomedical Ethics and Society
2525 West End Ave., Suite 400
Nashville, TN 37203

EBIHARA, Hideki, Ph.D. (*via teleconference*)
Staff Scientist
Disease Modeling and Transmission Section
Laboratory of Virology
Division of Intramural Research
Rocky Mountain Laboratories
National Institutes of Allergy and Infectious Disease
National Institutes of Health
903 South 4th Street
Hamilton, MT 59840

ELSWORTH, John D., Ph.D.
Professor
Yale University School of Medicine
Department of Psychiatry
300 George St., Suite 901
New Haven, CT 06511

FELDMANN, Heinrich, M.D., Ph.D. (*via teleconference*)
Chief
Laboratory of Virology
Division of Intramural Research
Rocky Mountain Laboratories
National Institute of Allergy and Infectious Diseases
National Institutes of Health
903 S. 4th Street
Hamilton, MT 59840

FREEMAN, Thomas B., M.D., F.A.C.S.
Professor
Department of Neurosurgery
University of South Florida
Harborside Medical tower
4 Colombia Drive, Suite 730
Tampa, FL 33620

TABAK, Lawrence A., D.D.S., Ph.D.
Director
National Institute of Dental and Craniofacial Research
National Institutes of Health
Building 31, Room 2C39
MSC 2290
31 Center Drive
Bethesda, MD 20892-2290

Nonvoting Agency/Liaison Representatives

National Science Foundation

Representative TBD

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

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

U.S. Department of Health and Human Services

Food and Drug Administration, Office of Cellular, Tissue, and Gene Therapies

TAKEFMAN, Daniel M., Ph.D.
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

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. Environmental Protection Agency

FREDERICK, Robert, Ph.D.
Program Manager
Office of Research and Development
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Mail Code 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
Mail Code 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

Manish K. Aghi, University of California, San Francisco (UCSF)
Ron L. Alterman, Mount Sinai School of Medicine
Pakwai Au, FDA, DHHS
Raymond Bartus, Ceregene, Inc.
Katherine Berkhausen, Food and Drug Administration (FDA), U.S. Department of Health and Human Services (DHHS)
Nicholas M. Boulis, Emory University School of Medicine
Christopher C. Broder, Uniformed Services University of the Health Sciences
Cheauyun Chen, FDA, DHHS
Ronald G. Crystal, Weill Medical College, Cornell University
Charles Davis, CSD Biostatistics Inc.
Wilson DeCamp, Parkinson Pipeline Project
Margaret Fishl, University of Miami School of Medicine
Debra Gessner, Tocagen Inc.
Harry Gruber, Tocagen Inc.
Ying Huang, FDA, DHHS
Douglas J. Jolly, Tocagen Inc.
Noriyuki Kasahara, University California, Los Angeles
Arifa Khan, FDA, DHHS
Jeffrey H. Kordower, Rush University
Arnold Kuzmack, Parkinson Pipeline Project
Carolyn Laurencot, National Cancer Institute (NCI), National Institutes of Health (NIH)
Andrea Loewen-Rodriguez, Ceregene, Inc.
William Marks, UCSF
Herbert Meltzer, Vanderbilt University (*via teleconference*)
Richard Morgan, NCI, NIH
C. Warren Olanow, Mount Sinai School of Medicine
Romelda Omeir, FDA, DHHS
Jeffrey M. Ostrove, Ceregene, Inc.
Keith Peden, FDA, DHHS
Dan Pertschuk, Tocagen Inc.
Steve Rosenberg, NCI, NIH
Mercedes Serabian, FDA, DHHS
Li Sheng, FDA, DHHS
Joao Siffert, Ceregene, Inc.
Mark Stacy, Duke University
Lawrence A. Tabak, National Institute of Dental and Craniofacial Research, NIH
Frank Tung, GeneCure Biotechnologies LLC
Frosso Voulgaropoulou, National Institute of Allergy and Infectious Diseases, NIH
Carol Weiss, FDA, DHHS

Attachment III Abbreviations and Acronyms

AAV	adeno-associated viral, adeno-associated virus
AAV-2	adeno-associated virus serotype 2
ACTG	AIDS Clinical Trial Group
AE	adverse event
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante
BSL	biosafety level
BWG	Biosafety Working Group (a subcommittee of the RAC)
CD	cytosine deaminase
cDNA	complementary deoxyribonucleic acid
CMV	cytomegalovirus
CNS	central nervous system
CTL	cytotoxic T cell
DBS	deep brain stimulation
DHHS	U.S. Department of Health and Human Services
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
<i>E. coli</i>	<i>Escherichia coli</i>
FDA	Food and Drug Administration, DHHS
GBM	glioblastoma multiforme
gc	genome copies
GLP	good laboratory practices
GTSAB	Gene Transfer Safety Assessment Board
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
IBC	institutional biosafety committee
IgG	immunoglobulin G
L-Dopa	levodopa
LINCL	late infantile neuronal ceroid lipofuscinosis
MLV	murine leukemia virus
MRI	magnetic resonance imaging
MTD	maximal tolerable dose
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
<i>NIH Guidelines</i>	<i>NIH Guidelines for Research Involving Recombinant DNA Molecules</i>
NTN	neurturin
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	Parkinson's disease
PET	positron emission tomography
PI	principal investigator
RAC	Recombinant DNA Advisory Committee
RCR	replication competent retroviral
RG	risk group
RML	Rocky Mountain Laboratories
RNA	ribonucleic acid
SAE	serious adverse event

SIV	simian immunodeficiency virus
SN	substantia nigra
STN	subthalamic nucleus
TH	tyrosine hydroxylase
TPP-1	tripeptidyl peptidase
UCSF	University of California, San Francisco
UPDRS	Unified Parkinson Disease Rating Scale
VSV-G	vesicular stomatitis virus type G
XMRV	xenotropic murine leukemia virus-related virus