RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 16, 2005

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

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]

March 16, 2005

The Recombinant DNA Advisory Committee (RAC) was convened for its 99th meeting at 8:00 a.m. on March 16, 2005, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Diane Wara (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:00 a.m. until 5:30 p.m. on March 16. The following individuals were present for all or part of the meeting.

Committee Members

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

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

Amy P. Patterson, Office of the Director, National Institutes of Health (NIH)

***Ad Hoc* Reviewers/Speakers**

Raymond T. Bartus, Ceregene, Inc.
Elaine S. Collier, National Center for Research Resources (NCRR), NIH
Ronald G. Crystal, New York Presbyterian Hospital/Cornell University
Howard J. Federoff, University of Rochester *(via teleconference)*
Theodore Friedmann, University of California, San Diego
Diane E. Griffin, Johns Hopkins University *(via teleconference)*
Richard A. Knazek, NCRR
Stephen J. Russell, Mayo Clinic
Mark H. Tuszynski, University of California, San Diego
Elias A. Zerhouni, NIH

[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. Borror, Office for Human Research Protections, U.S. Department of Health and Human Services (DHHS)
Stephanie L. Simek, U.S. Food and Drug Administration (FDA), DHHS

NIH Staff Members

Rosemarie Aurigemma, National Cancer Institute (NCI)
Robert Baughman, National Institute of Neurological Diseases and Stroke (NINDS)
Sandra H. Bridges, National Institute of Allergy and Infectious Diseases
Liza Dawson, John E. Fogarty International Center
Kelly Fennington, OD
Linda Gargiulo, OD
Dennis Hickstein, NCI
Tom Holohan, OD
Robert Jambou, OD
Laurie Lewallen, OD
Catherine McKeon, National Institute of Diabetes and Digestive and Kidney Diseases
R. Rita Misra, NCI
Karen Musynski, NCI
Marina O'Reilly, OD
Eugene Rosenthal, OD
Sonia Skarlatos, NHLBI
Karen Schweikart, NCI
Thomas Shih, OD
Danilo Tagle, NINDS
Anthony Welch, NCI
Gisele White, OD
Bradley C. Wise, National Institute on Aging

Others

There were 92 attendees at this 1-day RAC meeting. Attachment I contains a list of RAC members, *ad hoc* reviewers and speakers, and nonvoting agency and liaison representatives. Attachment II contains a list of public attendees.

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

Dr. Wara, RAC Chair, called the meeting to order at 8:00 a.m. on March 16, 2005. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* was published in the *Federal Register* on February 8, 2005 (70 FR 6720). Issues discussed by the RAC at this meeting included public discussions of three protocols, a data management report, updates of three protocols reviewed by the RAC in prior years, and a presentation on General Clinical Research Center (GCRC) resources for long-term follow-up. In addition, Dr. Elias Zerhouni, M.D., Director of NIH, presented the RAC with the Scientific Freedom and Responsibility Award from the American Association for the Advancement of Science.

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

II. Minutes of the December 16, 2004, RAC Meeting/Drs. Barkley and Gelehrter

Dr. Gelehrter stated that the minutes of the December 2004 RAC meeting had been well prepared and were complete and accurate, with a few minor typographical errors that had already been communicated to the OBA.

A. Committee Motion 1

It was moved by Dr. Gelehrter and seconded by Dr. Barkley that the RAC approve the minutes of the December 16, 2004, RAC meeting. The vote was 15 in favor, 0 opposed, and 0 abstentions.

III. Update on Human Gene Transfer Protocol #9906-322: A Phase I Study of Nerve Growth Factor (NGF) *Ex Vivo* Gene Therapy for Alzheimer's Disease (AD)

Presenter: Mark H. Tuszynski, M.D., Ph.D., University of California, San Diego

[Note: Dr. Wara noted that this update was presented as background for the review of Protocol #0501-689; see Section V below.]

Dr. Tuszynski reviewed the clinical results of this protocol to date, presenting the results of cognitive testing and positron emission tomography (PET) scan studies. He noted the findings are in press and will be published in the journal *Nature Medicine*. Dr. Tuszynski stated that nerve growth factor (NGF) therapy holds potential for treating progressive disorders of the nervous system. The premise on which this treatment is based is that the natural proteins of the brain prevent the death of and augment the function of responsive cell populations. In an adult monkey study, *ex vivo* NGF delivery protected cholinergic neurons, which degenerate and die in AD.

He presented an update of protocol 9906-322, which used a murine leukemia viral (MLV)-based vector system to transduce primary autologous fibroblasts in patients with AD. The fibroblasts were implanted into the nucleus basalis region of the brain to provide an *ex vivo* cell source for trophic support of degenerating neurons. The clinical assessment group included six subjects with a mean age of 67.1 years and a diagnosis of early, probable AD. Subjects were recruited in the early stages of the disease to allow for informed consent and because early intervention in the degenerative process holds better potential for neuroprotection. All subjects safely completed the cell injection procedure with the first two subjects received treatment on one side of the brain and the next four subjects received bilateral injections at escalating doses. Dr. Tuszynski noted that the outcomes should be interpreted cautiously, because the study is a small Phase I trial with no placebo controls and no blinding. Results indicated a statistically significant change in the rate of cognitive decline in mean Mini-Mental Status Examination scores. The PET scans of the subjects that received bilateral injections showed a significant increase in cortical activity following NGF delivery relative to the first baseline. This indicates a reversal of the expected pattern of decline over time for AD patients. Dr. Tuszynski reported that there have been no adverse events (AEs) from either the growth factor or the gene delivery system with follow-up from 2 to 4 years.

IV. Update on Human Gene Transfer Protocol #0401-623: A Phase I/II, Dose-Escalating, Randomized and Controlled Study to Assess the Safety, Tolerability, and Efficacy of CERE-110 (AAV-Based, Vector-Mediated Delivery of Beta-NGF) in Subjects with Mild to Moderate AD

Presenter: Raymond T. Bartus, Ph.D., Ceregene, Inc.

[Note: Dr. Wara noted that this update was presented as background for the review of Protocol #0501-689; see Section V below.]

Dr. Raymond Bartus noted that David Bennett, M.D. of Rush Medical College, is the principal investigator (PI) for this Phase I, dose-escalating trial. CERE-110 is a genetically engineered adeno associated virus serotype 2 (AAV-2) vector that expresses NGF in the nucleus basalis, the same target discussed by Dr. Tuszynski. The open-label trial has two dose levels with three subjects receiving each dose level. The study's primary purpose is to assess the safety and tolerability of the different doses of CERE-110 when administered to subjects with mild to moderate AD. Secondary objectives are to evaluate efficacy through assessment of cognitive functioning, using the Activities of Daily Living and Dementia Quality of Life scales, to determine the biodistribution of CERE-110 in urine and serum by PCR, and to evaluate immunogenicity by determining the antibody response to AAV and NGF. To date, three subjects have been enrolled and follow-up ranges from nine weeks to eight months. No AEs have occurred. Biodistribution data in serum and urine are negative.

Dosing of Cohort 1 was completed in January of 2005. A cumulative review of the data by the DSMB was held in March. Cohort 2 will be administered their first doses in April of 2005. In response to questions, Dr. Bartus clarified that the subjects were not prescreened for pre-existing AAV antibodies. He said the subjects in this trial were impaired to an extent similar to those in Dr. Tuszynski's trial. In closing, he noted that PET scans will be conducted later in the study, after a clinically meaningful time period has elapsed.

V. Discussion of Human Gene Transfer Protocol #0501-689: A Phase I, Open-Label Study of CERE-120 (AAV-2-NTN) to Assess the Safety and Tolerability of Intrastriatal Delivery to Subjects with Idiopathic Parkinson's Disease (PD)

Principal Investigator:	William J. Marks, Jr., M.D., University of California, San Francisco
Other Presenters:	Raymond T. Bartus, Ph.D., Ceregene, Inc.; Jeffrey H. Kordower, Ph.D., Rush Presbyterian-St. Luke's Medical Center; Paul S. Larson, M.D., University of California, San Francisco; C. Warren Olanow, M.D., Ceregene, Inc.; Jeffrey M. Ostrove, M.D., Ceregene, Inc.; Philip Starr, M.D., Ph.D., University of California, San Francisco
Sponsor:	Ceregene, Inc.
RAC Reviewers:	Drs. Bohn and Johnson and Ms. Kwan
Ad hoc Reviewer:	Howard J. Federoff, M.D., Ph.D., University of Rochester *(via teleconference)*

[Note: Drs. Lo, Muzyczka, Simari, and Wara recused themselves because of conflicts of interest. Dr. DeLuca chaired this portion of the RAC meeting.]

A. Protocol Summary

PD is a slowly progressive, neurodegenerative disorder that currently afflicts approximately 1 million people in the United States. PD is caused by the loss of function and death of dopamine neurons in the substantia nigra, a region of the brain that controls balance and coordinates muscle movement. Because these neurons no longer make dopamine and start to die, the lines of communication between the brain and the body become progressively weaker. Eventually, the brain is no longer able to direct or control muscle movement in a normal manner. The four primary symptoms of PD often appear gradually but increase in severity over time: (1) tremor or trembling in the hands, arms, legs, jaw, and face; (2) rigidity or stiffness in the limbs and trunk; (3) slowness of motor movements; and (4) postural instability or impaired balance and coordination. People with PD may have trouble walking, talking, or completing simple tasks that depend on coordinated muscle movements.

Treatment for PD currently aims at temporarily replenishing or mimicking dopamine's actions. However, as the disease progresses, the drugs gradually lose effectiveness and increasingly cause side effects such as uncontrolled movements. Importantly, no available therapy addresses the underlying cause of PD. Several neurotropic factors can augment the function of nigrostriatal dopaminergic neurons and protect them from degeneration. These factors include a family of proteins called glial cell line-derived neurotropic factor ligands such as glial cell line-derived neurotropic factor (GDNF) and neurturin (NTN).

GDNF and NTN share structural and functional similarities and demonstrate comparable beneficial effects in animal models of PD.

To be most safe and effective, neutrophic factor therapy should cover as much of the target area as possible with the therapeutic protein without affecting non-target sites. In non-clinical studies, CERE-120, an adeno-associated virus vector (AAV2) expressing NTN, has been shown to effectively deliver the neurotrophic factor to the nigrostriatal system and protect nigral dopaminergic neurons from degeneration in both rodent and non-human primate models of PD. The animal studies also have shown that CERE-120 administration is safe and well tolerated.

This proposed Phase I clinical trial will investigate the safety and tolerability of CERE-120 surgically delivered to the striatum of research participants with PD. Safety will be determined by evaluation of spontaneously reported adverse events, clinical laboratory test results, magnetic resonance imaging, neuropsychometric tests, and thorough clinical evaluations. All research participants will be monitored for signs of inappropriately targeted CERE-120 transduction or an immune reaction to the product. The primary enrollment criterion is a diagnosis of advanced PD. Participants also must have no other significant neurological or medical abnormalities contraindicating surgery or study participation. After completion of the study, all participants will undergo annual, lifelong monitoring.

The trial will include two cohorts of 12 to 18 subjects. The first cohort will receive doses of $2.0x10^{11}$ vector genomes (vg) and the second will receive $8.0x1^{11}$ vg, divided into four targeted locations per striatum. Initially, subjects will be enrolled sequentially, so that the second subject will be administered CERE-120 no less than 28 days after the first subject has undergone the dosing procedure. The third and fourth subjects will be treated no less than 28 days after the second subject has undergone the dosing procedure and the fifth and sixth subjects no less than 28 days after the fourth. At least 28 days after the sixth subject in the low-dose cohort has undergone the dosing procedure, the first subject in the high-dose cohort will be treated with CERE-120. Enrollment in the high-dose cohort will follow the same paradigm as that employed in the low-dose cohort.

Study assessments will be performed during a 30-day eligibility evaluation period, a baseline assessment (0 to 7 days before surgery), and during the surgical dosing procedure (day 0). For the first 28 days after surgery, subjects will visit the research facility approximately every 7 days after the completion of the dosing procedure, and thereafter at 2, 3, 6, 9, and 12 months. Adverse event assessments, clinical laboratory tests, and assessments of disease status will be performed at each visit. Clinical assessments of PD will be administered at the visits scheduled for months 1, 3, 6, 9, and 12. Long-term assessments will be performed annually thereafter.

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

Twelve RAC members voted for in-depth review and public discussion of the protocol. Key issues included the absence of a rescue strategy and the use of a novel neurotrophic factor that has not been used previously in the human brain in gene transfer research. RAC reviewers Drs. Bohn, Kwan, and Johnson and *ad hoc* reviewer Dr. Federoff submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Bohn read into the record a disclosure that one of her research interests relates to the development of regulated vectors for Parkinson's disease and that she is participating in a large, multi-center program funded by NINDS, for which Dr. Federoff is the PI. She noted that a good therapy for late-stage PD is needed and the protocol was the first one proposing to deliver a secretable growth factor to large areas of the brain. However, she expressed concern about the lack of an apparent rescue strategy to remove the NTN gene expression in the brain, especially since multiple brain areas are to be targeted and AAV2 vectors have been observed to be transported to non-targeted brain regions. Given that several PD trials involving GDNF protein delivery were stopped and cerebellar toxicity was detected in monkey studies, she asked the investigators to explain how they planned to respond should any adverse events result from NTN delivery which may persist for many years. She asked for more information on the supporting animal studies and their applicability to this protocol, the levels and distribution of NTN and the receptors

it would be acting through. She suggested that the use of eight needle tracks was aggressive surgically and reflected a design more compatible with a Phase II than a Phase I study. Regarding the inclusion of pro-NGF sequence in the NTN construct, she noted that studies have suggested that pro-NGF may induce neuronal cell death. She asked how much pro-NGF-NTN is produced and binds the receptors involved in cell death. Her additional concerns addressed the criteria for the possible addition of subjects to the cohorts, the need for a description of the evaluations of the autopsy material, the relationship of pre-immune antibodies to vector transduction. She requested an explanation for the detection of vector DNA in the cerebellum, brain stem, and lymph nodes in the absence of NTN mRNA expression.

Dr. Federoff asked whether the investigators had assayed for potentially novel biological properties of the pro-NGF-NTN construct, and for any immune responses to the new epitope created in the fusion protein. Regarding the potential for efficacy in late stage Parkinson's patients, he asked about the number of target cells and GFRα1 receptors still remaining at that disease stage. Dr. Federoff also asked about the sensitivity of the detection of trafficking of CERE-120 outside the nervous system. Because expression of CERE-120 may not have reached steady state levels at 28 days, Dr. Federoff asked for the rationale for the 28 day serial enrollment. Noting that both peak toxicity and the chronicity of the bioactive molecule should be of concern in toxicology studies, Dr. Federoff stated that none of the data presented addressed the longer-term toxicity that might accrue from accumulated and persistent bioactivity of NTN. He asked if the modeling done by the investigators was sufficiently predictive to give them confidence that a pro-inflammatory environment will not be created by a gene that can't be turned off.

Ms. Kwan stated that the non-technical abstract and the informed consent documents were well written, with technical terms kept to a minimum. She also noted that the documentation of the request for autopsy was one of the best that has been submitted to the RAC. However, based on some optimistic wording in the informed consent document, she expressed concern that subjects might anticipate a greater relief or treatment value from the protocol than is justified. She asked the investigators to clarify the wording to indicate whether the period between doses is 28 days. She asked for an expanded written explanation for the research subjects explaining that the expression of NTN can't be stopped because cells may be permanently changed when gene transfer is performed. Ms. Kwan requested that public discussion include an explanation as to why the introduction of the vector in this Phase I protocol should begin with such an extensive application and she wondered whether this attempt to try to obtain benefit was a paradigm shift away from the definition of Phase I research.

Dr. Johnson disclosed that he had invented two uses of AAV, a commercial-scale production of AAV vectors and a vaccine vector that was patented by his former employer and licensed to Targeted Genetics Corporation. His former employer receives royalties from Targeted Genetics Corporation and some royalty monies are passed on to him. Dr. Johnson noted that the protocol is provocative and complex, and since he's not a neurobiologist, he restricted his review primarily to the use of AAV as the vector for gene delivery, which he described as straightforward.

C. RAC Discussion

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

- Dr. DeLuca asked in which regions of the brain the clinical inoculations would take place.
- Dr. Federoff asked if there might be exuberant sprouting of neurons in places where the growth factor has been produced and is bioactive.
- Dr. Albelda asked why the investigators decided to use bilateral injections, since injecting one side only might be safer and provide an internal control for efficacy.
- Dr. Bohn asked the investigators to consider increasing the 28-day delay between cohorts.
- Dr. Vile inquired about the basis of the restriction of protein expression even with very high doses of the virus.

- Dr. Nemerow asked about the control in the MPTP monkey model and whether the investigators had ever tried empty vector as a control.

D. Investigator Response

Dr. Bartus and his colleagues responded to RAC questions and concerns with the following information:

- Regarding the lack of a rescue strategy, the investigators considered potential risks. Since no adverse events were observed in extensive nonclinical safety/toxicity studies, they considered hypothetical risks and the specific adverse effects associated with intraventricular administration of other growth factors. The investigators described the treatment strategies they considered specific and effective for symptoms that might arise. These include pharmacological treatments that have been effective in subjects who were administered GDNF. (GDNF is structurally and functionally similar to NTN.) Information on these potential risks will be provided to each subject in the informed consent document.

- In response to questions about the region of the brain selected, the investigators explained that it is a single targeted site, the nigrastriatal system. They initially considered one injection in the caudate and three in the putamen, but refined the protocol to focus only on the putamen. By injecting only into the anterior putamen, the investigators can infuse higher doses and lower the risk of the experimental material spreading to the ventricles. Based on volumetric and kinetic studies of NTN distribution, bilateral injections into four sites in each brain hemisphere was considered to provide the most appropriate test of safety. An extensive review of the literature indicates that a complication rate from needle tracks, such as hemorraghic strokes, is 1 to 3 percent, and these events are often transient. The investigators routinely implant eight needle tracks per side when conducting fetal nigra transplant studies and have not seen any side effects or complications in protocols similar to the one proposed.

- Regarding the retention of GFRα1 expressing neurons in late stage PD, there is a 55-60% loss of nigra neurons in late stage PD. The data are not specifically available on expression of GFRa1 in Parkinsons disease, however, in animal models that induce nigral neuronal degeneration, there are persistent trophic responses, presumably mediated by GFRa1. In other neurodegenerative disorders such as Alzheimer's disease, also characterized by progressive neuronal degeneration over time, growth factor receptors remain expressed well after the onset and progression of neuronal decline.

- Regarding the 28-day serial enrollment of participants, the investigators described the dosing schedule as a commonly used one and similar to that used in the protocol reviewed by the RAC the previous year for CERE-110. NTN expression reached maximal and stable levels by 28 days with no further increase up to seven months post-administration. No toxicity was detected in the rat studies out to one year and monkeys at seven months post-administration of the vector.

- Concerning the use of a pro-NGF-NTN fusion sequence, the study team stated that although NGF has been implicated in programmed cell death during development, GFLs such as NTN have not been shown to exert pro-apoptotic effects. Correspondingly, no evidence of cell death has been observed in any of the non-clinical studies conducted to determine the safety profile of CERE-120. The same pro-NGF sequence was expressed in the NGF vector used in the earlier trial in which pro-NGF was less than 1% of the expressed product and there was no evidence of neuronal injury.

- No cellular marker of inflammation or immune reaction in the brain, no humoral immune response to human NTN, and no change in hematology parameters were detected in any of the nonclinical studies in rats or monkeys. This empirical evidence, coupled with the data for long-term

expression of NTN (greater than 6 months), suggests that a significant immune response to the potential new fusion protein epitope did not occur.

- Although the *in vivo* half-life of CERE-120 derived NTN is unknown, the study team stated that non-clinical experiments did not detect NTN protein accumulation in the brain.
- The investigators have seen no evidence of sprouting.
- Consent for autopsy will be re-confirmed from the subject's relatives. The brain will be harvested quickly using standard procedures, hemisected, and placed in the Zamboni fixative. All brains will be shipped in the fixative to a central site for pathological examination. After immersion fixation is complete, standard neuroanatomical evaluation will be performed. Representative samples will be taken from the substantia nigra, striatum (with special attention to the putamen and areas of CERE-120 deposit), cortex, brainstem, cerebellum, and other areas as needed, and processed for histological evaluation. Immunohistochemistry for NTN and tyrosine hydroxylase, as well as evaluation for immunological responses will be performed.
- The criteria for adding as many as three subjects are: 1) A peri-operative complication that might preclude assessment of safety, tolerability, and potential efficacy at 6 months; 2) Intercurrent unrelated medical illness that might preclude assessment of safety, tolerability, and potential efficacy; and 3) WHO Grade 3 or 4 Toxicity in 1 of 6 subjects.
- The CERE-120 DNA detected in the absence of transcript signal in areas of the brain outside the target or in the draining cervical lymph nodes may be non-transcriptionally active fragments of DNA (extra-cellular particles of CERE-120, degraded DNA, etc.) that diffused from the target injection site. The assay amplifies a 110 bp fragment of CERE-120 and these DNA species are indistinguishable from transcriptionally active genomes present in transduced cells. The sporadic presence of CERE-120 RNA in the brain stem results from a dissection artifact where parts of the substantia nigra were occasionally included in the brain stem samples. The substantia nigra is expected to contain transcriptionally active CERE-120 genomes resulting from the transport of vector particles from the striatum.
- Regarding the questions about the effect of pre-existing immunity to AAV2, three of the macaques studied had pre-existing AAV2 antibodies, but no correlation was observed between antibody levels and subsequent volume of NTN distribution.
- The control animals received formulation buffer or the vector expressing GFP, a reporter gene.
- The pharmacology studies of CERE-120 indicate that NTN distribution can be controlled by manipulating the CERE-120 dose. Neither the AAV2 vector nor NTN protein diffuse far from the site of injection allowing some control in targeting sites.
- The investigators made all suggested changes to the informed consent document.

E. Public Comment

Joan I. Samuelson, a PD patient for 18 years, and president of the Parkinson’s Action Network, discussed the real-life circumstances experienced by PD patients and potential PD research participants. She noted the urgent need for an effective therapy for PD and that most PD patients would accept significant risks for the possibility of benefits. Ms. Samuelson offered her remarks as part of the presentation by Drs. Olanow and Bartus.

Dr. Borror noted two places in the informed consent document that referred to gene transfer as “treatment.” She suggested that that language be altered, to which the investigators agreed.

F. RAC Recommendations

Dr. DeLuca summarized the following RAC comments and recommendations:

- Due to concerns about potential adverse effects of unintended expression of the neurotrophic factor neurturin (NTN) in non-targeted areas, the location of the injection sites is a critical safety issue. As written, the protocol does not accurately describe the location of the injection sites and it is difficult to assess the risk of unintended expression without this key information.

- Recent studies suggest that precursors of nerve growth factors may be biologically active. Since the pro sequence from nerve growth factor is encoded in the CERE-120 NTN construct, data demonstrating how Pro-NTN is processed in neurons following injection of CERE-120 into striatum should be submitted.

- The protocol proposes to inject CERE-120 into only one area of the brain—the terminal sites of the dopaminergic neurons. A preclinical study in a non-human primate model of Parkinson's disease should be conducted to assess the efficacy of this approach. The study could be conducted in either the MPTP treated monkey model or the aged monkey model. If the MPTP treated monkey model is used, the single injection site should be to the putamen (i.e., it should not be the substantia nigra, as was done in Experiment CR-0413). If the aged monkey model is used, the injection site should be the terminal regions of the dopaminergic neurons, and the efficacy data should be collected at least up to six months after injection. In either case, the efficacy data should be statistically significant, i.e., they should demonstrate that CERE-120 has effects on dopaminergic neuronal morphology and fluorodopa levels as seen through PET imaging.

- The likelihood that NTN will be expressed for years in the targeted areas and the lack of a rescue strategy is a safety concern. Data from non-human primate studies addressing this concern should be submitted. The data should demonstrate whether long-term NTN expression causes toxicities and inflammatory effects at the injection site. The data should encompass a full year of observation.

- Data demonstrating the sensitivity of the assay used to detect the NTN protein in the biodistribution studies should be provided.

- In view of lack of a rescue strategy in the protocol, the investigators will undoubtedly be extremely vigilant about monitoring for adverse events and, if they do occur, will take appropriate steps to modify the protocol as needed. However, out of an abundance of caution, consideration should be given to modifying the protocol to allow more than 28 days to elapse before the study agent is administered to the next subject.

- In the informed consent document, make it clear that: 1) the protocol lacks a rescue strategy that would allow the transgene to be removed and/or turned off; 2) the vector and the transgene will remain, and remain potentially active in the brain indefinitely; and 3) the treatment of any adverse effects that occur does not constitute a "rescue " strategy.

- Delete language in the informed consent document that could mislead prospective research participants about the experimental nature of the study, including language that characterizes the study agent as a treatment. Words such as "intervention " or "study agent" or "experimental agent" should be used instead. For further information, please refer to the *NIH Guidelines on Informed Consent in Gene Transfer Research* at http://www4.od.nih.gov/oba/rac/ic//>>

G. Committee Motion 2

It was moved by Ms. Kwan and seconded by Dr. Nemerow that the recommendations summarized orally by Dr. DeLuca be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 12 in favor, 0 opposed, 0 abstentions, and 4 recusals (Drs. Wara, Lo, Simari, and Muzyczka).

VI. Discussion of Human Gene Transfer Protocol #0501-691: Phase I Trial of Systemic Administration of Edmonston Strain of Measles Virus, Genetically Engineered to Express Sodium Iodide Symporter (NIS), with or without Cyclophosphamide, in Patients with Recurrent or Refractory Multiple Myeloma (MM)

Principal Investigators:	Angela Dispenzieri, M.D., Mayo Clinic, and Morie A. Gertz, M.D., Mayo Clinic
Presenter:	Stephen J. Russell, M.D., Ph.D., Mayo Clinic College of Medicine
Other Presenters:	Eva Galanis, M.D., Mayo Clinic; David Dingli, M.D., Mayo Clinic; Mark J. Federspiel, Ph.D., Mayo Clinic; Kah-Whye Peng, Ph.D., Mayo Clinic; Karen Schweikart, Ph.D., NCI
RAC Reviewers:	Drs. Albelda, Dewhurst, and Lo
Ad Hoc Reviewer:	Diane E. Griffin, M.D., Ph.D., Johns Hopkins University *(via teleconference)*

[Note: Drs. DeLuca, Simari, and Heslop (Dr. Heslop did not attend this RAC meeting) recused themselves because of conflicts of interest.]

A. Protocol Summary

MM is a type of bone marrow cancer caused by the proliferation of malignant plasma cells. It is estimated that almost 15,000 patients will be diagnosed this year in the United States with MM and that the disease will be responsible for 11,000 deaths. Despite significant advances in the understanding of MM and the introduction of new therapeutic approaches such as high-dose chemotherapy with bone marrow transplantation, the disease remains incurable. Relapse after stem cell transplantation is the rule, and survival is not significantly prolonged. The median survival of patients with MM is 3 to 4 years.

Recombinant measles viruses derived from the Edmonston vaccine strain have been used to treat a variety of tumors in animal models. The rationale behind the use of these viruses is their potent and selective oncolytic effect on tumor cells while leaving normal cells relatively unharmed. The basis for this tissue selectivity is the over-expression of CD46 by myeloma cells, the receptor that is preferentially utilized by the virus for cell entry. In addition, measles virus vaccines have an exceptional safety record since they have been given to millions of people worldwide with minimal toxicity and very rare mortality. Recently a recombinant measles virus was engineered that induces Sodium Iodine symporter (NIS) expression in infected cells (MV-NIS). NIS is a plasma membrane protein that is physiologically expressed in a variety of tissues but mainly in the thyroid gland. NIS concentrates iodide ions in cells against an electrochemical gradient and provides the basis for radioiodide therapy of well-differentiated thyroid malignancies. MV-NIS retains the potent and selective oncolytic activity of the parent virus but in addition induces NIS expression. This allows the repeated and non-invasive monitoring of viral gene expression using ^{123}I followed by gamma camera imaging. In addition, in vivo studies show that MV-NIS has potent oncolytic activity against a variety of myeloma tumor cell lines.

This protocol proposes to explore the use of escalating doses of MV-NIS in a Phase 1 trial for participants with relapsed or refractory multiple myeloma. The study objectives are (1) to determine the safety and toxicity of the intravenous administration of MV-NIS without or with cyclophosphamide in patients with relapsed or refractory multiple myeloma, (2) to determine the maximum tolerated dose of MV-NIS administered intravenously, (3) to determine the time course of viral gene expression and elimination and the biodistribution of virally infected cells at various times points after virus administration using ^{123}I gamma camera imaging, (4) assess viremia, viral shedding and viral persistence after intravenous administration, (5) monitor the humoral immune response to the virus and (6) explore the anti-myeloma efficacy of the

virus using standard myeloma response criteria. The protocol is divided in two stages. During Stage 1, MV-NIS will be administered alone in escalating doses starting from $Ix10^6$ $TCID_{50}$ up to $I x 10^9$ $TCID_{50}$. The presence of pre-existing anti-measles immune responses might interfere with delivery of MV-NIS to myeloma cells. Thus in Stage 2 of the protocol participants will be pre-treated with intravenous cyclophosphamide that can suppress the immune response to the virus and allow more efficient infection and propagation of the virus in myeloma cells. In participants who are pre-treated with cyclophosphamide, the starting dose of virus will be 100-fold less than the MTD and slowly escalated in 3-fold increments with subsequent cohorts. Participants will be followed by radioiodine imaging and regular estimation of monoclonal protein levels to assess any anti-myeloma activity.

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

Thirteen RAC members voted for in-depth review and public discussion of the protocol. Key issues included the novelty of the vector, and the history of rare instances in which measles vaccination resulted in disseminated measles in immunocompromised hosts.

Dr. Albelda stated that his major overall concern was safety, noting the risk of giving a replicating virus to immunocompromised participants and in stage two of the study, increasing the immunocompromised state by administering cyclophosphamide (Cytoxan) prior to vaccination. He requested detailed results from the ongoing clinical trial using the related MV-carcinoembryonic antigen (CEA) virus, including a description of the manufacturing process, viral shedding and biodistribution data, clinical responses and adverse events. Dr. Albelda also requested additional discussion about the rationale for using Cytoxan. He asked what efforts would be made to quantify the amount of CD46 on the myeloma cells of each research participant before gene transfer in order to possibly determine a threshold level needed for efficacy. Regarding the informed consent document, he suggested that participants should be informed of the risk of tumor lysis syndrome (TLS), since this was postulated to have occurred in some of the animal models.

Dr. Dewhurst requested more information on the expression of CD46 by MM tumors: the percentage of tumor cells that overexpress, how the range of expression levels overlapped with CD46 expression in normal cells, and whether baseline expression could be correlated to efficacy. He asked the investigators to discuss the current biosafety containment level used for the production and handling of the MV-NIS product, and requested data on the stability of MV-NIS in human cells, including MM cells. He asked for the rationale for administering cyclophosphamide only 2 days prior to delivery of MV-NIS. He asked for more detail on the proposed assays for measuring anti-MV antibody levels in research participants, and to detect virus-shedding. Dr. Dewhurst also asked the investigators whether they were concerned that, if the therapy were to be effective, TLS might occur and whether the antimeasles immune globulin would be immediately available onsite if problems were to arise.

Dr. Lo asked several questions about the use of the participants' stored samples, including whether the samples would be stripped of all identifiers, whether the participants could refuse to have their samples used for additional research, and under what circumstances the use of the stored samples would not be considered human subjects research (e.g., after the participant's death); he also requested clarification of the process by which participants' samples could be used by researchers from other institutions. Dr. Lo expressed concern about the dose of Cytomel in relation to the risk of cardiac adverse effects, including arrhythmias and angina, in a population whose age puts them at risk for coronary artery disease.

Dr. Griffin asked for additional information as to whether expression of CD46 is related to the substantial variability in MV-induced death of myeloma cells and whether normal plasma cells are susceptible to MV-induced cell death. She requested more information on the four participants dosed with MV-CEA. She also asked for the evidence for a rapid decrease in MV antibody after dosing with cyclophosphamide. For the mouse and monkey models, she suggested studying previously immunized animals to more closely replicate the situation in the research participants who would have previously received the measles vaccine. She asked for more details of the monkey studies.

C. RAC Discussion

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

- Dr. Gelehrter asked whether expression of the NIS gene in the vector could be used to track and treat tumors, with appropriate thyroid protection for the participants.
- Dr. Johnson wondered about the possible occurrence of TLS if this clinical trial were successful. Dr. Lo added that TLS can be problematic with hyperkalemia, hyperphosphatemia, and renal failure.

D. Investigator Response

Dr. Russell and his colleagues responded to RAC questions and concerns in the written reviews and during the discussion with the following information:

- Regarding the safety of administration of a replicating vector to immune compromised participants, the measles vaccine has been given safely to individuals with immune deficiency following transplantation or HIV infection. Post-exposure prophylaxis with anti-measles immune globulin has been effective in controlling viral proliferation in a neonatal population and in controlling measles virus induced complications in adults. Ribavirin will also be used as an additional antiviral agent in participants with adverse effects due to persistent MV-NIS replication. The Mayo Clinic Pharmacy has a supply of anti-measles immune globulin as well as ribavirin in stock and available for immediate use if clinically required.
- The ongoing clinical trial using the MV-CEA vector has enrolled four participants. No dose limiting toxicity was observed. Transient viremia occurred in two participants.
- The purpose of using cyclophosphamide prior to therapy with MV-NIS is to delay the cellular immune response and provide additional time for the virus to spread in the tumors. While cyclophosphamide will not acutely decrease anti-measles virus antibodies, it can decrease the anamnestic response
- CD46 expression on plasma cells isolated from the bone marrow aspirates will be taken at the time of enrollment and again on the subsequent bone marrow biopsy taken 6 weeks after the end of therapy
- The informed consent form will be modified to note that tumor lysis syndrome was suspected in animal studies and is a possible complication of therapy with MV-NIS. The investigators noted that TLS is very rarely observed in MM patients, even in the context of a rapid response. Participants will be watched carefully for any signs of TLS, their electrolytes will be followed carefully, and they will be encouraged to drink plenty of fluids.
- Although the level of CD46 over-expression varies among myeloma cells isolated from different patients, data show that CD46 is always significantly over-expressed compared to non-neoplastic mononuclear cells isolated from these patients or healthy controls.
- Regarding containment, measles viruses that contain only genes encoding reporter or marker proteins (e.g., green fluorescent protein, secreted carcinoembryonic antigen) are considered Risk Group1/Biosafety Level1. Any other MV recombinant with a gene encoding a biologically active protein is used at BL2.

- The design of the monkey study will not provide efficacy information because the monkeys have not been immunized; however, since this study is primarily a safety study in monkeys that do not have prior exposure to the virus, the investigators can test the worst-case scenarios.

- Dr. Russell agreed to modify the protocols to include the use of a test for antibodies that neutralize the MV. The assay for measuring anti-measles virus antibodies is an enzyme linked immunoassay for IgG available from DiaMedix. Functional virus neutralizing assays will be performed using a Vero cell assay that is currently under development.

- In response to Dr Lo's concerns regarding the proposed dose of cytomel and recently published data from breast cancer trial, the protocol was modified to decrease the dose of cytomel to 25mcg twice a day starting 4 days before therapy with MV-NIS. The cytomel is used to suppress thyroidal NIS expression and thus limit iodide uptake in the thyroid. This will enhance the quality of the imaging and minimize toxicity to the thyroid from iodide. The trial will also exclude patients with coronary artery disease and dysrhythmias such as paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation.

- The oncolytic activity of MV strains has been studied in a number of myeloma cell lines and the neoplastic plasma cells of 18 myeloma patients. The virus was uniformly oncolytic to these cells, all of which over-expressed CD46. The variable responses observed in the severe combined immunodeficiency disease (SCID) mouse model were due to differences in susceptibility of the xenografts, which is not related to receptor expression. This may be due to anatomical disparities in the vascular supply of the different tumors, allowing differing efficiencies of entry of virus into the tumor parenchyma, or to extracellular matrix interfering with virus spread that is more evident in certain tumor types than in others.

- The investigators have not studied the susceptibility of normal plasma cells to the virus, but the destruction of normal plasma cells is not a major concern since these cells can be regenerated from memory B cells after virus clearance. Also, agammaglobulinemic patients with no functional plasma cells are able to live a normal life with monthly immunoglobulin replacement therapy. Furthermore, most myeloma patients have significant hypogammaglobulinemia due to suppression of normal plasma cells and the infectious risks associated with this aspect of the disease are a well established component of routine myeloma care.

- Regarding handling of participant samples, if participants disallow the use of sample for future research, the samples would be used for the study as indicated, and discarded.

- Because of the inclusion of the NIS transgene in the vector, one of the potential outcomes of this proposed trial could be that iodine would be taken up within the tumors, which would be seen in the course of the imaging studies. If that occurs and the vector is ineffective in reducing tumor size as a single agent, the follow-on study would add iodine 131 to boost any therapeutic effect.

E. Public Comment

Dr. Borror suggested a few revisions to the informed consent document, including complex and technical language and characterizations of gene transfer as "therapy" or "treatment." Dr. Dispenzieri agreed to edit the document accordingly.

F. RAC Recommendations

Dr. Wara summarized the following RAC comments and recommendations:

- It is not clear whether the measles antibody levels seen in the mouse model are comparable to the levels that are likely to occur in humans. Because humans will have pre-existing immunity to measles virus and it is possible that pre-existing neutralizing antibodies might influence the efficacy and/or safety of the proposed gene transfer, a neutralizing antibody assay should be developed and used to assess antibody levels in research participants.

- Because the effectiveness of the proposed gene transfer could be influenced by the expression levels of CD46 on the tumors, the levels of CD46 expression should be determined prior to, and at appropriate time points after, vector administration.

- The reading level of the informed consent document is too high and should be simplified. Complex and technical terms, such as “intravenous,” should not be used.

- The informed consent document uses terms such as “treatment” that may mislead prospective subjects about the potential benefits of participation. The term “treatment” should be replaced with “experimental agent” or “study agent.” For further information, please refer to the NIH Guidance on Informed Consent for Gene Transfer Research http://www4.od.nih.gov/oba/rac/ic.

G. Committee Motion 3

It was moved by Dr. Lo and seconded by Dr. Gelehrter that the recommendations summarized orally by Dr. Wara be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 13 in favor, 0 opposed, 0 abstentions, and 3 recusals (Drs. Wara, Lo, Simari, and Muzyczka).

VII. Data Management Report/Drs. Albelda, Heslop, Simari, and Wara

Dr. Simari reported that there had been 11 protocol submissions since December 2004, 8 of which were not selected for public review. Of the 8 trials not selected for public review, 7 were for cancer, and 1 was for peripheral artery disease; 4 of these trials employed plasmid-based vector systems, 2 employed an adenoviral vector, 1 employed a herpes simplex vector, and 1 employed a fowlpox viral vector.

Between November 4, 2004, and February 1, 2005, 165 AEs were reported to the OBA. Of these AEs, 9 were Type A events, 7 of which were classified as A1, which is defined as serious, possibly associated, and unexpected; all of the A1 events were reviewed in detail by Drs. Albelda, Heslop, Simari, and Wara. Of those 7, Dr. Simari mentioned 1 trial in detail: Protocol #0004-393, a Phase II study of tumor cell vaccine for non-small cell lung cancer (NSCLC) using a transforming growth factor-beta-2 antisense gene-modified allogeneic tumor cell vaccine in patients with stages 2 to 4 NSCLC. It was reported that a 53 year-old participant with NSCLC developed chronic myelogenous leukemia following dosing. This participant had received 16 of 16 injections of the investigational vaccine, with the last administration in June 2004. In November 2004 this individual had a white blood cell count of 448,000 with prominent bands. Following a bone marrow biopsy, the diagnosis was made of chronic myelogenous leukemia. A Philadelphia chromosome was present and the participant started Gleevec on November 30, 2004. The study sponsor and investigators were undergoing a detailed genetic analysis regarding the presence and timing of the Philadelphia chromosome. Those studies are currently under way, and the RAC expects to receive additional information about this participant.

Dr. Wara reported that 142 protocol amendments had been submitted in the past 3 months, of which 35 were PI or site changes, 3 were protocol design modifications, 17 were protocol status changes, 50 were annual updates, 16 were responses to M-I-C(1) of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, and 21 were other modifications or amendments. A total of 39 annual updates and/or safety reports were filed. She briefly discussed issues related to the following four protocols:

- **#0201-516, *Ex Vivo* Retroviral Gene Transfer for Treatment of X-Linked SCID.** On November 24, 2004, the U.S. protocol investigators learned through communication with the research group at Necker Hospital in Paris, France, that one of two participants with X-SCID who had developed leukemia as a result of gene transfer had died of leukemia. The U.S. investigators revised their informed consent document to reflect that death, and the revised form was approved by the institutional review board (IRB) on December 23, 2004. On January 24, 2005, the U.S. investigators informed the RAC of a third case of lymphoproliferative disorder in an X-SCID participant who had received gene transfer in the French study and that the U.S. site would place its trial on voluntary clinical hold until further guidance was provided by the U.S. Food and Drug Administration (FDA), the OBA, and the IRB.

- **#0210-557, An Open-Label, Dose-Escalation Study to Assess the Safety of AMG001 Administered via Intramyocardial Injection Catheter in Patients with Ischemic Heart Disease Nonamenable to Coronary Artery Bypass Graft or Percutaneous Coronary Intervention.** This protocol underwent indepth review and public discussion during the December 2002 RAC meeting. At that time, the RAC recommended that the study be redesigned without a placebo arm which may have posed an unjustifiable risk to the research participants in the placebo group. In the M-I-C(1) response, the investigators amended the clinical protocol to remove the use of a placebo control from the study design and the title of the study was changed. The RAC also recommended that the qualifications and role of the independent reviewers determining participant eligibility at each site be carefully defined in terms of their functions and any conflict of interest potential; the investigators carried out this recommendation.

- **#0307-593, A Phase I, Open-Label Study of Intrastriatal Infusion of AAV Encoding Human Aromatic L-Amino Acid Decarboxylase in Subjects with Advanced PD.** This protocol underwent RAC public review on October 17, 2003. In the M-I-C(1) response, the investigators extended the period of time between cohorts from the 30 days originally proposed to 4 months to allow a more thorough evaluation of AEs before dose escalation to the next cohort. The exclusion criteria were modified to specify eligible baseline AAV antibody titers. Histology results from the nonhuman primate studies that had been ongoing during the public RAC discussion were reported as showing no significant histopathology beyond mild gliosis localized to the needle tracks. The informed consent document was modified to include the wording “May not be possible to remove the transgene safely."

- **#0312-619** *(discussed below in Section XI)*, **Administration of a Replication-Deficient, AAV Gene Transfer Vector Expressing the Human CLN2 cDNA to the Brain of Children with Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL).** This protocol was not selected for indepth and public RAC review on January 20, 2004. The first participant was enrolled on May 31, 2004. The RAC received a letter dated January 21, 2005, in follow-up to the serious AEs and death of a participant following status epilepticus after receiving gene transfer. Multiple modifications to the protocol include:

  (1) Baseline and serial electroencephalograms (EEGs) were added to the protocol to help evaluate occult seizure activity before and after gene transfer.

  (2) The protocol timeline has been revised to include serial EEGs at baseline and after gene transfer at 17 days, 6 months, and 18 months. The results of these EEGs were added to the safety and efficacy parameters.

  (3) The informed consent document was modified to inform potential participants and their families of the status epilepticus and subsequent death of a participant. The informed consent document now states, "In November 2004 a research subject enrolled in this protocol died after having episodes of multiple seizures. We are unable to determine whether the cause of the child's seizures was due to the natural history of the disease, the surgical procedure and/or drug administration in the setting of the disease, the research study drug (biological vector), or some combination thereof."

(4) The informed consent document was further modified by the addition of anticipatory guidance to the parents. The parents of the participant who died apparently delayed reporting the child's seizure activity for 30 hours. Thus, a new statement in the informed consent document reads: "If you detect any significant changes in your child's condition after discharge from the hospital, we recommend that you contact your health care provider immediately."

(5) Additional AEs were reported in this participant, including anemia, constipation, and reddening of the groin area. The protocol and the informed consent document were amended to include these risks.

VIII. Presentation of the American Association for the Advancement of Science (AAAS) Award to RAC Members

Presenter: Elias A. Zerhouni, M.D., Director, NIH

Dr. Zerhouni presented the RAC with the American Association for the Advancement of Science (AAAS) Scientific Freedom and Responsibility Award, which he had accepted on behalf of the RAC at the AAAS annual meeting in Washington, D.C. in February 2005. The RAC received the award "[f]or providing outstanding leadership and enabling society to proceed with recombinant DNA research and genetic therapy in a responsible manner, thereby enhancing the opportunities presented by modern genetic advances." Dr. Zerhouni noted that the award is usually given to individual scientists or engineers. He stated that it was an inspired choice on the part of the AAAS to give the award to the RAC's cohort of scientists and public members, as they have contributed significantly to the history of science. Dr. Wara accepted the award from Dr. Zerhouni on behalf of the RAC.

IX. General Clinical Research Center (GCRC) Resources for Long-Term Followup

Presenters: Elaine S. Collier, M.D., National Center for Research Resources (NCRR), NIH, and Richard Knazek, M.D., NCRR contractor

Dr. Knazek presented the NCRR program developed to facilitate efforts by PIs, sponsors, or institutions to provide long term follow-up for research participants in gene transfer trials. Long term follow-up is necessary to maximize protection of participants in gene transfer protocols and to increase the understanding of the mechanisms by which adverse events occur.

The FDA currently requires applicants for all gene transfer investigational new drugs (INDs) whose protocols were approved after October 1, 2001, to describe their plan to comply with the Biological Response Modifiers Advisory Committee recommendations to:

- Provide annual physical examinations for the first 5 years following infusion of the vector or vector-treated cells.
- Acquire data annually for years 6 to 15 via mailed questionnaires regarding autoimmune, hematopoietic, or neurological disease or new malignancies.
- Check participants in retroviral studies for the presence of replication-competent retrovirus every 3 months during the first year; blood must be archived annually thereafter.
- Send the resulting data to the FDA.

The FDA currently requires investigators holding INDs for retroviral transduction of hematopoietic stem cells to:

- Provide lifelong annual clinical evaluations.
- Perform laboratory studies to detect the development of clonal cell populations semiannually for the first 5 years and annually for the following 10 years. If clonality is observed, the integration site should be determined, and a second test should be performed no more than three months later.
- Send the resulting data to the FDA.

Compliance with these guidelines is relatively straightforward when the supporting grant is active and remains funded. However, when grant support ends, it becomes more challenging to ensure proper follow-up. To address this problem, NCRR has developed a program offering support for follow-up visits at general clinical research centers (GCRC).

Future NIH Notice of Grant Awards for clinical gene transfer studies will state, in part, that

> "…the NIH acknowledges that the clinical gene therapy protocol to be supported by this award will require an Investigational New Drug (IND) number and that the Food and Drug Administration currently requires that all recipients of a gene transfer product be followed clinically for 15 years. Should this grant expire prior to completion of the required followup, the National Institutes of Health will facilitate efforts of the principal investigator-sponsor and his/her grantee institution to meet their regulatory responsibilities by offering support for followup visits for these patients when examined at a General Clinical Research Center (GCRC)…."

Investigators and their institutions were informed of the program in a January 2004 *NIH Guide* Notice. Although advisory because the NIH cannot issue directives to a grantee beyond the duration of a grant, the notice reminded the grantee institution of its obligation to follow FDA guidelines and suggested that the institution make every effort to provide follow-up care even after the grant terminates. To facilitate this, the NCRR will cover the cost of examining research participants if the visits occur at a GCRC, and the GCRC will provide outpatient clinic space, nursing, relevant routine laboratory tests, phlebotomy, and shipment of blood for assay and/or storage. It would be the responsibility of the grantee institution to contact the participant and provide support for travel to the GCRC. If such participants were to be followed outside of a GCRC, it would be the responsibility of the institution to support this long-term followup through internal, private, or other sources of funding. NCRR support would not be provided if the trial had been sponsored by industry. Although GCRC resources could be used in these circumstances, it would be the responsibility of the institution to obtain reimbursement from the sponsor according to GCRC guidelines. PIs are requested to use the consent process to inform participants about the requirements and the processes involved in conducting long-term follow-up studies. The purpose of this initiative is to help protect participants by detecting AEs that may arise long after participation in a gene transfer protocol—and its grant support—has ended.

In addition, Dr. Knazek noted that the National Gene Vector Laboratory (NGVL) at Indiana University will serve as the site for long-term blood sample storage and will collaborate with Dr. von Kalle of Cincinatti Children's Hospital to provide clonality testing for stem cells transduced with retroviruses. The NCRR will cover the costs associated with storage and clonality testing by supplements to the NGVL cooperative agreement.

X. Discussion of Human Gene Transfer Protocol #0411-681: Phase Ia/Ib Trial of Anti-Prostate-Specific Membrane Antigen (PSMA) Designer T Cells in Advanced Prostate Cancer after Nonmyeloablative (NMA) Conditioning

Principal Investigator: Richard Paul Junghans, M.D., Ph.D., Roger Williams Hospital
RAC Reviewers: Drs. Powers, Rosenberg, and Wara
Ad Hoc Reviewer: Theodore Friedmann, M.D., University of California, San Diego

[Note: Ms. Kwan recused herself because of a conflict of interest.]

A. Protocol Summary

Chimeric immunoglobulin T cell receptors (IgTCR) are fusion products of the antibody (ab) binding domain with the signaling chain of the TCR. When expressed by gene transfer techniques in recipient T cells, the resulting "designer T cells" are redirected by the IgTCR to attack tumors expressing the surface antigen (Ag) recognized by the Ab. The immunotherapy approach against prostate cancer to be used in this protocol will combine the specificity of the Ab against prostate specific membrane antigen (PMSA) with the cytotoxic potency of T cells. The strategy is designed to bypass a major drawback of cancer immunotherapy approaches, which have been hampered by the fact that most tumor antigens are normal self-proteins to which the patient is already tolerized.

Previous Phase I trials of designer T cells against diverse antigens have provided evidence that designer T cells experienced limited survival after trafficking to the tumor, without sustained proliferation, with time-limited side-effect and benefit profiles, irrespective of IL2 supplementation. When mature T cells are infused in the nonmyeloablative (NMA) setting, those T cells expand to fill the hematopoietic space and persist indefinitely. This study will test the tolerance and toxicity of designer T cells infused in the NMA setting and their ability to reconstitute as a stable proportion of circulating T cells. The extended survival of antitumor designer T cells by this strategy is expected to correlate with improved patient responses and extended patient survival. Research participant T cells will be transduced *ex vivo* with a retroviral vector expressing anti-PMSA IgTCR to create to designer T cells. These cells are returned to the participant after NMA conditioning by intravenous administration, and the participant will be followed for toxicity and response.

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

Three RAC members voted for in-depth review and public discussion of the protocol. Key issues included the higher-than-usual dose of Cytoxan, the risk of retroviral insertional mutagenesis, and the uncertainty of the risk-benefit ratio.

Dr. Powers requested that the informed consent document be modified to reflect a third instance of leukemia in the French X-SCID trial and to indicate the risk of autoimmune disease. He also asked the investigators to provide additional details on the plan for long-term follow-up. Dr. Powers suggested deleting the follow-up timeframe of 10 years because it might give participants false expectations of living that long.

Given that a subset of participants in the French X-SCID trial subsequently developed leukemia following administration of cells transduced with a retroviral vector, Dr. Rosenberg stressed the importance of assessing the risks of long-term persistence and expansion of the transduced cells. She requested that the investigators discuss the multiplicity of infection (MOI) expected to be achieved, an assessment of the proviral copy number per cell in the populations to be infused, and a sensitive method of monitoring the persistence of infused cells. Dr. Rosenberg also requested that the investigators discuss procedures to determine whether expansion of a single clone is occurring in any of the recipients, given that high doses of cells infected at high multiplicity will be infused increasing the risk of insertional mutagenesis. Because the NMA regimen used prior to infusion, coupled with the interleukin-2 (IL-2) dosing, may allow the infused cells to persist, she noted the importance of discussing how each of these procedures might influence engraftment of the cells and development of lymphoma. Dr. Rosenberg also suggested discussion about the investigators' plans to evaluate the immunogenicity of some of the murine sequences they plan to use as well as to evaluate the homeostatic expansion of T cells that could lead to autoimmunity.

Because of similarities between the effects of NMA conditioning and X-SCID, Dr. Wara asked the investigators to consider the risk-benefit ratio of using high-dose Cytoxan. She also asked about the possibility of including a suicide gene in the vector. If available, an animal model should be used to study the designer T cells along with the IL-2 proposed following NMA conditioning. Regarding the possibility of

clonality, Dr. Wara requested information about the investigators' plans for monitoring and archiving of samples. In the event clonality is detected, she asked about the treatment strategy to be used and the methods for analyzing vector integration. Regarding the informed consent document, she suggested that the investigators specify the duration of follow-up after the study ends and the frequency of blood draws, modify the risks section to include the three instances of leukemia and one death in children in the French X-SCID trial, include the risk of autoimmune disease, and include standard language regarding request for autopsy.

Dr. Friedmann expressed concern that this approach recapitulates some of the features of the X-SCID study, in that it represents hematopoietic repopulation of a large number of retrovirally transduced cells into an immuno-compromised participant in whom strong selection pressure is applied in favor of survival of the transduced cells. He asked whether the number of independent initial integration events had been determined and whether studies could be designed to identify the minimum number of integration events and transduced cells that could produce the desired degree of re-population. He also asked whether animal studies are available in which retroviral vector-transduced cells have been grafted into animals with and without NMA conditioning to test the possibility that the greater efficiency of cell engraftment after NMA treatment also allows more effective growth of tumorigenic cells resulting from an insertional mutagenic event. He suggested the investigators consider incorporating into the vector suicide elements or other gene expression regulatory elements to allow shutdown or reversal of gene expression or destruction of transduced cells in the event of clonal selection and development of leukemia.

C. RAC Discussion

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

- Given that a large number of transduced cells might persist for long durations, Dr. Rosenberg wondered whether the investigators had information on the frequency with which the cells might be stimulated to divide as a consequence of an immune response or of some other event during the participant's life.
- Dr. Vile wondered about the possibility of additional animal testing that might shed light on the persistence of the T cells.

D. Investigator Response

Dr. Junghans and his colleagues responded to RAC questions and concerns in the written reviews with the following information:

- Regarding the survival time of the infused cells and the percentage of infused cells that persist over time in the individual, engraftment occurs when the T cells are introduced into a vacated space created by the chemotherapy, and these cells may be expected to be with the individual for life. These cells may account for 10 percent of the person's total T cells.
- In response to Dr, Rosenberg's question as to the frequency with which the transduced cells would be stimulated to divide, Dr. Junghans replied that the only factor that distinguishes the transduced cells from the rest of the participant's T cells is their specificity for PSMA. The only time the cells will be stimulated will be in response to the presence of the prostate tumor, so if the tumor cells are eliminated, the transduced T cells will not proliferate, and will die from activation of induced cell death after stimulation.
- With 10-60% T cell transduction, the most probable number of insertion events per transduced cell is one.
- The incorporation of suicide elements in the vector would add a xenoantigen that may be targeted for immune destruction resulting in the elimination of the modified cells. The simpler

vector would be preferable until efficacy is proven in the study. Additional strategies could be considered later in the event that adverse events are observed.

- Development of a suitable animal model to test the designer T cells plus IL-2 following NMA conditioning would be difficult because of the short life span of mice (< 2 years) and small number of T cells (10^8 cells) at risk.

- A satisfactory mouse model to test T cell persistence also does not exist because human stem cells and T cells do not reconstitute in mice.

- Regarding archiving of samples and followup after the study ends, Dr. Junghans stated that the FDA guidelines require archiving at 3 months, 6 months, 1 year, and then annually for 10 years. The investigators will archive samples at those time points and suggested it would be reasonable to go further and take and archive samples every 3 months while the participant is alive. In the event of detection of a clonal expansion, the participant will be monitored for leukemia and treated with chemotherapy appropriate for the participant.

- The murine sequences in the IgTCR are a possible target for immune responses, and this will be monitored by serum reactivity and cellular responses. Like murine antibodies that have been used in human therapies, such a reaction could abrogate effectiveness of the therapy, but is unlikely to constitute a health risk to the patient.

- Dr. Junghans agreed to include the risk of autoimmune disease in the informed consent document and to include standard language regarding a request for an autopsy.

E. Public Comment

Dr. Simek summarized the FDA's requirements for long-term follow-up for retroviral vector gene transfer. A research participant must be monitored the first 5 years by annual physical examination and then 6 to 10 years after that using a questionnaire. An FDA guidance document states that replication-competent retroviral samples must be taken at 3-month periods for the first year, and if they are negative, subsequent samples are archived for the lifetime of the participant. The FDA is currently working on a long-term follow-up guidance document, so this requirement may change. With regard to clonality, the FDA asks all sponsors of retroviral clinical trials to provide a plan for monitoring clonality. Studies involving stem cells are monitored more closely because they involve proliferating cells. All investigators should include in their protocols at least a brief outline addressing a monitoring plan.

Dr. Borror recommended that language such as “treat” and “treatment” in the informed consent document be changed so as not to imply the possibility of clinical benefit. In addition, some language was overly complex and should be simplified.

F. RAC Recommendations

Dr. Wara summarized the following RAC comments and recommendations:

- The use of retroviral vectors to transduce hematopoietic cells of even transiently immunocompromised subjects in an *ex-vivo* gene transfer model raises concerns similar to those posed by the French X-SCID study. In particular, the potential for increased proliferation and persistence of the transduced T cells, especially in conjunction with use of nonmyeloablative (NMA) preconditioning, may pose risk and the extent of this potential risk should be assessed in an ongoing manner.

- The NMA preconditioning may increase the likelihood of long term engraftment of the transduced T cells and therefore, possibly increase risk of tumorigenesis. Consideration should be given to

developing an appropriate animal model in which to conduct preclinical studies to assess the effect of NMA preconditioning on long term engraftment of the transduced cells.

- Since the vector to be used in the trial is a retrovirus, there is a risk of insertional mutagenesis and subsequent development of leukemia or other serious adverse events, as occurred in the French X-SCID study. Cell samples should be obtained at the onset of the study and at appropriate times thereafter to permit an assessment of the number and changing patterns of vector insertions in the cell population and the possible emergence of clonal populations of cells.

- The oncogenic potential of the transgene should be assessed in suitable *in vivo* animal studies in which the tumorigenic potential of cells expressing the transgene can be examined.

- Consideration should be given to developing measures to enhance the safety of the retroviral vector, such as through the use of suicide or ablation elements.

- The reading level of the informed consent document is too high and should be simplified. The informed consent document uses such terms as "treatment" that may mislead prospective research participants about the potential benefits of participation. The term "treatment" should be replaced with "experimental agent" or "study agent." The informed consent process should also refer to the third case of leukemia and death of one of the research participants. For further information, please refer to the NIH Guidance on Informed Consent for Gene Transfer Research http://www4.od.nih.gov/oba/rac/ic.

G. Committee Motion 4

It was moved by Dr. Albelda and seconded by Dr. Powers that the recommendations summarized orally by Dr. Wara be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 15 in favor, 0 opposed, 0 abstentions, and 2 recusals (Ms. Kwan and Dr. Nemerow).

XI. Update and Discussion of Human Gene Transfer Protocol #0312-619: Administration of a Replication-Deficient AAV Gene Transfer Vector Expressing the Human CLN2 cDNA to the Brain of Children with LINCL (Batten Disease)

Presenter: Ronald G. Crystal, M.D., New York Presbyterian Hospital/Cornell University

Dr. Crystal was invited to the meeting to review a serious adverse event (SAE) resulting in the death of one participant, address the measures and monitoring plans instituted to try to prevent such an event in the future, and address the complex social, ethical, and fiscal issues surrounding the funding of a trial from private resources.

Batten disease is an autosomal recessive lysosomal storage disorder that affects 1 in 2 million births. Affected children are healthy at birth and develop normally until ages 2 to 4; death occurs between the ages of 8 and 12 years, after the children become vegetative because of brain atrophy and loss of neurons over time. The disorder is caused by mutations in the CLN2 gene affecting a protease involved in removal of waste proteins. Accumulation of waste proteins in the lysosomes leads to cell death, particularly affecting neurons and retinal pigment epithelia. The disease was a candidate for gene transfer because even if only a low number of target cells are transduced, the gene product is secreted from those cells and can cross correct other cells. The AAV vector was administered into the brain through six burr holes

To date, four individuals have been dosed in the clinical study, all with the same drug dose. Research participant 6 developed recurrent seizures that evolved into status epilepticus and died 49 days post-administration of the gene transfer. In response to the SAE, the investigators have been examining the data of all four participants in terms of their seizure scores during the screening study, administration

sites, operative and postoperative management, and reviewing the inclusion/exclusion criteria, management of risks, monitoring and followup, seizure medications, and use of EEGs.

On the basis of discussions with the FDA, modifications were made to the protocol regarding consent and enrollment and issues related to the participation. Participant enrollment will be staggered by a minimum of 1 month. Antiseizure medications will be monitored prior to vector delivery and after vector delivery on days 7 and 14 and at 1 month, 6 months, and 18 months. Participants will also receive continuous EEG monitoring. Language was added to the informed consent document, in boldface, stating, "If you detect any changes in your child's condition after discharge from the hospital, we recommend that you contact your health care provider immediately." In addition, the investigators will contact the parents of the research participants on a daily basis after discharge to find out how they are faring.

Dr. Crystal discussed several ethical issues related to consent, enrollment, and funding. Enrollment is decided by a committee whose primary appointments are outside of Dr. Crystal's department. A clinical research monitor, who is separate from regulatory affairs and clinical operations, conducts monitoring, and there is also an independent medical safety monitor. Monitoring is conducted through the NIH GCRC at the New York Presbyterian Hospital, which provides research subject advocates.

The clinical study is funded by the Nathan's Battle Foundation (40 percent), the NIH GCRC (3 percent), and the Department of Genetic Medicine at the New York Presbyterian Hospital (57 percent). Dr. Crystal discussed the strategy developed to ensure that the clinical study and enrollment are not influenced by the Foundation that is funded, in part, by families with children with a rare disease. The funds from the Foundation are gifted to the university. The Foundation has no control over the use of the funds for the preclinical and clinical studies or participant enrollment.

A. RAC Discussion

Drs. Dewhurst, Powers, and Wara had reviewed the amendments to the protocol and assembled a list of questions that were provided to Dr. Crystal. Those questions were addressed during Dr. Crystal's presentation.

Dr. Wara noted that rare disease foundations can be formed through the resources of families seeking cures and this raises issues when there are expectations that potential treatment will be first accessible to family members rather than adhering to inclusion criteria to determine enrollment in a trial. Dr. Crystal suggested one possible public policy method of dealing with orphan diseases such as LINCL would be to establish nonprofit pharmaceutical companies based on different technologies—small molecules, monoclonal antibodies, gene transfer, and so forth—into which the foundations could then put their monies. These nonprofits would separate the finances from the research, thus reducing possible conflicts of interest, and also develop an infrastructure to avoid having to repeat safety and other preliminary studies.

XII. Closing Remarks and Adjournment/Dr. Wara

Dr. Wara thanked the participants and adjourned the meeting at 5:30 p.m. on March 16, 2005.

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

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Amy P. Patterson, M.D.
RAC Executive Secretary/OBA Director

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

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

Date: ________________

____
Diane W. Wara, M.D.
Chair

Attachment I
Recombinant DNA Advisory Committee Roster

Chair

WARA, Diane W., M.D.
Professor of Pediatrics
School of Medicine
Program Director
Pediatric Clinical Research Center
University of California, San Francisco
Room M-679
505 Parnassus Avenue
San Francisco, CA 94143-3466

Members

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

BARKLEY, W. Emmett, Ph.D.
Director of Laboratory Safety
Howard Hughes Medical Institute
4000 Jones Bridge Road
Chevy Chase, MD 20815-6789

BOHN, Martha C., Ph.D.
Professor
Medical Research Institute Council
Director
Neurobiology Program
Children's Memorial Institute for Education and Research
Northwestern University
Room 321
2430 North Halsted Street
Chicago, IL 60614-4314

DELUCA, Neal A., Ph.D.
Professor
Department of Molecular Genetics and Biochemistry
School of Medicine
University of Pittsburgh
Biomedical Science Tower, Room E1257
Pittsburgh, PA 15261-2072

DEMETS, David L., Ph.D.
Professor and Chair
Department of Biostatistics and Medical Informatics
University of Wisconsin Medical School
Box 4675
Clinical Sciences Center, Room K6/446A
600 Highland Avenue
Madison, WI 53792-4675

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

GELEHRTER, Thomas D., M.D.
Professor and Chair
Department of Human Genetics
University of Michigan Medical School
Buhl Building, Room 4909
Box 0618
1241 East Catherine Street
Ann Arbor, MI 48109-0618

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

JOHNSON, Jr., Philip R., M.D.
Chief Scientific Officer
Edmond F. Notebaert Endowed Chair in Pediatric Research
Director
Joseph Stokes Jr. Research Institute
The Children's Hospital of Philadelphia
Leonard and Madlyn Abramson Pediatric Research Center, Room 1216B
34th Street and Civic Center Boulevard
Philadelphia, PA 19104

KWAN, Terry, M.S.Ed.
Independent Collaborator
TK Associates
61 Highland Road
Brookline, MA 02445-7052

LO, Bernard, M.D.
Professor of Medicine
Director
CAPS Ethic Core
Program in Medical Ethics
School of Medicine
University of California, San Francisco
Room C-126
521 Parnassus Avenue
San Francisco, CA 94143-0903

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

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

POWERS, Madison, J.D., D.Phil.
Director
Kennedy Institute of Ethics
Georgetown University
37th and O Streets, NW
Washington, DC 20057

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

SIMARI, Robert D., M.D.
Professor of Medicine
Chairman for Cardiovascular Research
Mayo Clinic and Foundation
Guggenheim Building, Room 942C
200 First Street, SW
Rochester, MN 55905-0002

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

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

OBA Director/RAC Executive Secretary

PATTERSON, Amy P., M.D.
Director
Recombinant DNA Program
Executive Secretary
NIH Recombinant DNA Advisory Committee
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 20892-7985

AD HOC REVIEWERS AND SPEAKERS

BARTUS, Raymond T., Ph.D.
Senior Vice President, Research and Development
Chief Operating Officer
Ceregene, Inc.
Suite 130
9381 Judicial Drive
San Diego, CA 92121

COLLIER, Elaine S., M.D.
Deputy Director
Division of Clinical Research Resources
National Center for Research Resources
National Institutes of Health
U.S. Department of Health and Human Services
1 Democracy Plaza, Room 918
MSC 4874
6701 Democracy Boulevard
Bethesda, MD 20892-4874

CRYSTAL, Ronald G., M.D.
Chairman
Department of Genetic Medicine
New York Presbyterian Hospital
Weill Medical College
Cornell University
Box 96
1300 York Avenue
New York, NY 10021

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

FRIEDMANN, Theodore, M.D.
Professor of Pediatrics
Director
Human Gene Therapy Program
Whitehill Professor of Biomedical Ethics
School of Medicine
University of California, San Diego
Center for Molecular Genetics, Room 132
Mail Stop Code 0634
9500 Gilman Drive
La Jolla, CA 92093-0634

GRIFFIN, Diane E., M.D., Ph.D.
(via teleconference)
Professor and Chair
Bloomberg School of Public Health
Johns Hopkins University
615 North Wolfe Street
Baltimore, MD 21205

KNAZEK, Richard A., M.D.
Contractor
Division of Clinical Research Resources
National Center for Research Resources
National Institutes of Health
U.S. Department of Health and Human Services
1 Democracy Plaza, Room 910
MSC 4874
6701 Democracy Boulevard
Bethesda, MD 20892-4874

RUSSELL, Stephen J., M.D., Ph.D.
Director
Molecular Medicine Program
Mayo Clinic College of Medicine
200 First Street, SW
Rochester, MN 55905

TUSZYNSKI, Mark H., M.D., Ph.D.
Professor
Department of Neurosciences
University of California, San Diego
Basic Science Building, Room 4046
Mail Code 0626
9500 Gilman Drive
La Jolla, CA 92093

ZERHOUNI, Elias A., M.D.
Director
National Institutes of Health
U.S. Department of Health and Human Services
Building 1, Room 126
MSC 0148
1 Center Drive
Bethesda, MD 20892-0148

NONVOTING AGENCY REPRESENTATIVES

U.S. Department of Health and Human Services, U.S. Food and Drug Administration

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

Office of Therapeutics Research and Review

SIMEK, Stephanie L., Ph.D.
Deputy Director
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

LIAISON REPRESENTATIVE

JONES, Daniel P., Ph.D.
Senior Program Officer
Division of Research Programs
National Endowment for the Humanities
Room 303
1100 Pennsylvania Avenue, NW
Washington, DC 20506

Attachment II
Public Attendees

Renier Brentjens, Memorial-Sloan Kettering Cancer Center
Joy A. Cavagnaro, Access BIO, L.C.
Erika Check, *Nature*
Theresa Chen, FDA
Margaret Crowley, Eberlin Reporting Service
David Dingli, Mayo Clinic
Angela Dispenzieri, Mayo Clinic
Mark Federspiel, Mayo Clinic
Hannah Flaks, Henry M. Jackson Foundation for the Advancement of Military Medicine
Eva Galanis, Mayo Clinic
Mehdi Gasmi, Ceregene, Inc.
David R. Higgins, BioMedica, Inc.
Eugene Johnson, Washington University
Richard P. Junghans, Roger Williams Hospital
Jeffrey H. Kordower, Rush Presbyterian-St. Luke's Medical Center
Paul S. Larson, University of California, San Francisco
Daniel Lee, Ceregene, Inc.
Ruth Ryan Lessard, Avigen
Lee-Cheng Liu, AnGes MG, Inc.
Zhifeng Long, AnGes MG, Inc.
Andres M. Lozano, Toronto Western Hospital
Jinhua Lu, SAIC-Frederick, Inc.
Tianci Luo, Advanced Vision Therapies, Inc.
Maritza McIntyre, FDA
C. Warren Olanow, Ceregene, Inc.
Sheryl Osborn, Consultant
Jeffrey M. Ostrove, Ceregene, Inc.
Richard Peluso, Targeted Genetics Corporation
Kah-Whye Peng, Mayo Clinic
Glenn F. Pierce, Avigen
Susan M. Pond, Johnson & Johnson Research
Sheryl Ruppel, SAIC-Frederick, Inc.
Joan I. Samuelson, Parkinson's Action Network
Jude Samulski, University of North Carolina, Chapel Hill
Bruce Schneider, FDA
Mercedes Serabian, FDA
Michele M. Shoonmaker, Congressional Research Service
Geoff Symonds, Johnson & Johnson Research
Lorne B. Teichman, Johnson & Johnson
Ian Toma, George Washington University
Robert Zalaznick, Cornell University

Attachment III
Abbreviations and Acronyms

AAAS	American Association for the Advancement of Science
AAV	adeno-associated virus
AAV-2	adeno-associated virus serotype 2
AD	Alzheimer's disease
AE	adverse event
BRMAC	Biological Response Modifiers Advisory Committee
CEA	carcinoembryonic antigen
DNA	deoxyribonucleic acid
EEG	electroencephalogram
FDA	U.S. Food and Drug Administration
GCRC	General Clinical Research Center
IL-2	interleukin-2
IND	investigational new drug
IRB	institutional review board
LINCL	late infantile neuronal ceroid lipofuscinosis
MM	multiple myeloma
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTD	maximum tolerable dose
MV	measles virus
NBF	Nathan's Battle Foundation
NCRR	National Center for Research Resources
NGF	nerve growth factor
NGVL	National Gene Vector Laboratory
NIH	National Institutes of Health
NIS	sodium iodide symporter
NMA	nonmyeloablative
NSCLC	non-small cell lung cancer
NTN	neurturin
OBA	NIH Office of Biotechnology Activities
PD	Parkinson's disease
PET	positron emission tomography
PI	principal investigator
PSMA	prostate-specific membrane antigen
RAC	Recombinant DNA Advisory Committee
TLS	tumor lysis syndrome
SCID	severe combined immunodeficiency disease
X-SCID	X-linked severe combined immunodeficiency disease