RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

September 9-10, 2008

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]

September 9-10, 2008

The Recombinant DNA Advisory Committee (RAC) was convened for its 114th meeting at 12:30 p.m. on September 9, 2008, at the National Institutes of Health (NIH), Natcher Building, Room E1-E2, Bethesda, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 12:30 p.m. until 6:10 p.m. on September 9 and from 8:15 a.m. until 4:30 p.m. on September 10. The following individuals were present for all or part of the September 2008 RAC meeting.

Committee Members

David Alland, University of Medicine and Dentistry of New Jersey *(via teleconference)*
Jeffrey S. Bartlett, Nationwide Children's Hospital/The Ohio State University
Hildegund C.J. Ertl, The Wistar Institute *(present on Day 2 only)*
Hung Y. Fan, University of California, Irvine
Howard J. Federoff, Georgetown University Medical Center
Jane Flint, Princeton University *(present on Day 2 only via teleconference)*
Joseph A. Kanabrocki, The University of Chicago
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation
Bernard Roizman, The University of Chicago
Prediman K. Shah, Cedars-Sinai Medical Center *(via teleconference)*
Robyn S. Shapiro, Medical College of Wisconsin
Nikunj V. Somia, University of Minnesota, Twin Cities
Scott E. Strome, University of Maryland
Lee-Jen Wei, Harvard University
David A. Williams, Children's Hospital Boston/Harvard Medical School *(present on Day 1; via teleconference on Day 2)*
James R. Yankaskas, The University of North Caroline at Chapel Hill
John A. Zaia, City of Hope

Office of Biotechnology Activities (OBA)

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

***Ad Hoc* Reviewers and Speakers**

Roberto Cattaneo, Mayo Clinic *(via teleconference)*
Bradley T. Hyman, Harvard Medical School/Massachusetts General Hospital
Priya Kishnani, Duke University Medical Center *(via teleconference)*
Donna Przepiorka, Food and Drug Administration (FDA), U.S. Department of Health and Human Services (DHHS)

Nonvoting Agency Representatives

Kristina C. Borror, Office for Human Research Protections, DHHS
Daniel M. Takefman, FDA, DHHS

[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.

NIH/OD/OBA Staff Members

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

Others

There were 101 attendees at this 2-day RAC meeting.

Attachments

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

I. Day 1 Call to Order and Opening Remarks

Dr. Federoff, RAC Chair, called the meeting to order at 12:30 p.m. on September 9, 2008. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on August 18, 2008 (73 FR 48222). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (a subcommittee of the RAC), public review and discussion of five protocols, an update of the RAC's Biosafety Working Group's consideration of changes to the *NIH Guidelines* regarding noncontemporary human influenza and highly pathogenic avian influenza, two FDA regulatory updates regarding foreign trials for investigational new drugs (INDs) and guidance on current good manufacturing practice for Phase I trials, and discussion of the role of the RAC with regard to single-participant human gene transfer trials.

Dr. Corrigan-Curay reminded RAC members of the rules of conduct that apply to them as special Federal Government employees, read into the record the conflict of interest statement, and suggested that related questions be addressed to the OBA committee management officer. She noted that the new RAC members had already participated in NIH committee member training.

II. Gene Transfer Safety Assessment Board

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

Dr. Strome reported that of the 10 protocol submissions received by the OBA in the past 3 months, 5 were not selected for public review at this RAC meeting. All five of the protocols not selected were for cancer.

A total of 137 amendments were reported during this 3-month period, including 31 principal investigator (PI) or site changes, 56 annual reports, and 42 others (changes in status and protocol design modifications). One *Appendix M-I-C-1* review was discussed briefly.

Dr. Strome discussed the adverse events (AEs) that were reported to the OBA during this reporting period. A total of 140 AEs were reported from 21 trials, of which the overwhelming majority were

unrelated to the gene transfer products; there were 42 initial and followup reports in which the AE was possibly related to the gene transfer products. The Gene Transfer Safety Assessment Board reviewed 34 initial and followup AEs, including 14 initial reports and 20 followup reports that were submitted by investigators and sponsors from 11 trials. Three of those AEs were deemed to merit summary discussion at this RAC meeting:

A dose-limiting toxicity was reported in Protocol #0704-853: "A Phase I, Open-Label, Dose-Escalation, Multiple-Dose Study of the Safety, Tolerability, and Immune Response of CRS-207 in Adult Subjects with Solid Tumors Who Have Failed or Who Are Not Candidates for Standard Treatment." The participant was in the highest dose cohort of the CRS-207, which is a live attenuated strain of *Listeria monocytogenes (Lm)* expressing the human mesothelin gene. The *Lm* platform is the same as the platform proposed for Protocol #0807-932, reviewed on Day 2 of this RAC meeting. The trial's Data and Safety Monitoring Board (DSMB) reviewed the toxicity event, and the study site has implemented new monitoring and stopping rules in response to this event.

The OBA received notice that enrollment and dosing of participants in Protocol #0504-708: "A Phase III, Randomized, Open-Label Study of Docetaxel in Combination with CG1940 and CG8711 versus Docetaxel and Prednisone in Taxane Naive Patients with Metastatic Hormone Refractory Prostate Cancer" was stopped immediately after an independent DSMB reviewed safety issues and recommended halting participant enrollment and dosing due to an observed imbalance in deaths between the two treatment arms of the study. This study compares gene transfer in combination with docetaxel compared with docetaxel and steroid in participants with metastatic hormone refractory prostate cancer who are on narcotic medications for pain. To date, the study has enrolled 408 patients. The DSMB based its recommendation to halt enrollment on 114 deaths, 67 of which occurred in the gene transfer plus docetaxel combination treatment arm and 47 occurred in the docetaxel and steroid arm. A specific cause for the imbalance in deaths has not been identified, and the DSMB reported no new safety issues for the gene transfer vaccine when administered in combination with docetaxel. The sponsor will continue to follow participants enrolled in this trial and will analyze the clinical data to attempt to understand this difference, including baseline characteristics and prognostic factors as well as other dosing variables.

The second Phase III trial using the same vector is under way—Protocol #0405-653: "A Phase III, Randomized, Open-Label Study of CG1940 and CG8711 versus Docetaxel and Prednisone in Patients with Metastatic Hormone Refractory Prostate Cancer Who Are Chemotherapy Naive Compared to Gene Transfer Vaccine Alone to Docetaxel and Prednisone." In this protocol, the participants do not have pain that requires strong narcotic medications. The DSMB meeting included routine safety review of this protocol and did not recommend cessation of treatment of the participants currently remaining in the maintenance treatment phase of the trial. The informed consent document is being updated to ensure that all participants are made aware of the observation in Protocol #0504-708.

III. Discussion of Human Gene Transfer Protocol #0807-927: Phase I Translational Trial of Oncolytic Virotherapy with Recombinant Vesicular Stomatitis Virus (rVSV(MΔ51)-M3) by Hepatic Arterial Delivery in Patients with Primary Hepatocellular Carcinoma or Metastatic Colorectal Carcinoma in the Liver

Principal Investigators:	Savio L.C. Woo, Ph.D., and Max W. Sung, M.D., Mount Sinai School of Medicine
RAC Reviewers:	Drs. Fan, Kahn, and Zaia
Ad hoc Reviewer:	Roberto Cattaneo, Ph.D., Mayo Clinic *(via teleconference)*

Dr. Strome recused himself from consideration and discussion of this protocol due to a conflict of interest.

A. Protocol Summary

Oncolytic vesicular stomatitis virus (VSV) is being developed as a novel therapeutic agent for cancer treatment. VSV is sensitive to type I interferons and its replication in normal cells is suppressed by a robust type I interferon response. This response is attenuated in most cancer cells, which makes virus replication tumor-selective. While effective in killing most rodent and human cancer cells *in vitro*, wild-type VSV is nevertheless toxic in animals when administered systemically at doses higher than its maximum tolerated dose (MTD). Its safety can be substantively improved by a single amino acid deletion in its matrix protein (MΔ51), which does not alter the replication efficiency of the virus *in vitro*, but abolishes the M protein's activity in suppressing cellular mRNA transport from the nucleus to the cytosol. However, VSV(MΔ51) induces a much greater, robust cellular inflammatory response in the host than wild-type VSV, which severely attenuates its oncolytic potency *in vivo*. We have reported that the oncolytic potency of wild-type VSV can be substantially enhanced by vector-mediated expression of a heterologous viral chemokine binding gene that suppresses cellular inflammatory responses in the lesions.

To develop an effective and safe VSV vector for cancer treatment, investigators tested the hypothesis that the oncolytic potency of VSV(MΔ51) could be substantively elevated by vector-mediated expression of M3, a broad-spectrum and high-affinity chemokine-binding protein from murine gammaherpesvirus-68. The recombinant vector, rVSV(MΔ51)-M3, was constructed and used to treat rats bearing multifocal lesions (1-10mm in diameter) of hepatocellular carcinoma (HCC) in their liver by hepatic artery infusion. Treatment led to a significant reduction of neutrophil and natural killer cell accumulation in the lesions, a logarithmic elevation of intratumoral viral titer, substantially enhanced tumor necrosis and prolonged survival of the animals with a 50% cure rate. Importantly, there were no apparent systemic and organ toxicities in the treated animals. These results indicate that the robust cellular inflammatory responses induced by VSV(MΔ51) in the lesions can be overcome by vector-mediated M3 expression, and that rVSV(MΔ51)-M3 can be developed as an effective and safe oncolytic agent to treat patients with advanced HCC in the future. This vector has also been shown to be effective at replicating in and killing colorectal cancer cells in the liver of mice.

The investigators propose to test the safety of the vector in a Phase I Translational Trial of Oncolytic Virotherapy with a Recombinant Vesicular Stomatitis Virus rVSV(MΔ51)-M3 by Hepatic Arterial Delivery in Patients with Primary Hepatocellular Carcinoma or Metastatic Colorectal Carcinoma in the Liver using escalating doses of the virus, with the entry dose being three logs below the maximum tolerated dose in tumor-bearing rats. Prior to conducting the clinical trial a comprehensive bio-distribution study in HCC-bearing rats will be performed to determine the tissues most susceptible to VSV infection and demonstrate clearance of viable virus and vector genome over time, and a pharm-tox study in normal rats to determine short- and long-term vector-related toxicities.

B. Written Reviews by RAC Members

Eleven RAC members voted for in-depth review and public discussion. Key issues included that (1) VSV has not been used as an oncolytic virus in gene transfer, (2) the proposed construct contains a murine viral gene for a chemokine-binding protein that confers new immunomodulatory properties, and (3) the importance of public discussion of the safety of this new construct delivered by hepatic arterial injection, especially in light of the significant toxicity observed at the highest dose in preliminary pharmacology/toxicology studies in normal rats.

Three RAC members and the *ad hoc* reviewer provided written reviews of this proposed Phase I trial. Dr. Federoff summarized Dr. Kahn's review at this meeting because Dr. Kahn was unable to attend.

Noting that approval of this protocol at this time might be premature due to the absence of preclinical data addressing several points involving risks to participants, Dr. Fan asked whether the molecular basis for the resistance to interferon (IFN) in tumor lines is understood adequately and to what extent rVSV(MΔ51)-M3 is genetically stable. He suggested that toxicity studies in an animal model larger than the rat would seem important, given the concern about basing the dosing in humans on the rat preclinical data only, particularly since the vector is lethal at the rat MTD. Regarding the investigators' statement that a

significant fraction of humans have been exposed to VSV, Dr. Fan asked what effect prior exposure might have on the experimental therapeutic, whether rats with prior exposure to VSV had been tested for vector efficacy, and whether the presence of antibodies to VSV should be considered in the eligibility criteria. Because the protein to be used is a broad-spectrum inhibitor of innate immunity, Dr. Fan queried the investigators as to whether there is any evidence in the animal model for vector modulation of immune responses to other infectious agents and whether the investigators had conducted any tests of sensitivity to secondary infections. He asked to what extent human genetic variations in the IFN response pathway might affect the resistance of normal tissue to the vector. Noting that the investigators plan to administer the recombinant VSV into the hepatic artery with temporary blockage to allow virus uptake into the tumors, Dr. Fan requested that that procedure be described more clearly in the clinical protocol and that it be mentioned in the informed consent document, including duration of the blockage, how it would be induced, and what risks are associated with such a procedure in humans with compromised liver function.

Dr. Kahn limited his review to the informed consent document. He noted that the phrase "your study doctor" is used throughout the document and that the phrase is confusing as to whether it refers to the local investigator who is also the participant's physician. Dr. Kahn cautioned the investigators about overstating the possibility of effectiveness in this early-phase research, as currently written in the section explaining the purpose of this study. Although blood draws for laboratory testing are mentioned in numerous locations within the consent document, he suggested that a description of these tests be included. Dr. Kahn noted no mention of a request for autopsy and reminded the investigators that such a request is a requirement of *Appendix M*. He questioned the necessity of a second signature box for legal representatives (located on the final page of the informed consent document), since children and mentally challenged individuals are excluded from participation in this trial.

Dr. Zaia asked the investigators to address the potential use of this experimental agent in treatment-naive individuals, especially in view of the availability of FDA-approved chemotherapy for liver cancer, and to justify the potential inclusion of participants with preexisting anti-VSV antibodies. Because the innate immune mechanisms of control of VSV form the basis of this experimental therapy, Dr. Zaia requested that the investigators consider adding to the study characterization of the various natural-killer (NK) functions that might contribute to the protection from disseminated VSV. He requested that the investigators also consider adding functional clearance measurements as a dynamic marker for liver function. Noting that Dr. Woo is a co-PI, Dr. Zaia asked the investigators to enumerate the management plan for the conflict of interest regarding participant enrollment, assessment of AEs, and interpretation of data. With regard to the participant risks listed in the informed consent document, Dr. Zaia asked whether there is a potential for tumor lysis syndrome (given the preclinical results and that participants may have as much as 40 percent of the liver involved with tumor), asked what is known about the potential for M3 expression to alter the expected pathogenicity of VSV, and noted that the concomitant medications taken by participants in the upper age range of eligibility (up to age 85 years) could result in adverse effects. Dr. Zaia asked the investigators to indicate in the section on termination of participation that at certain times during this study it would be unwise for a participant to leave the study because of potential public health considerations related to spreading the virus.

Noting that the rat preclinical data are convincing, *ad hoc* reviewer Dr. Cattaneo asked whether a similar effect could be expected in humans—whether a chemokine-binding protein that is evolutionarily adapted to a rodent host would bind to primate chemokines with equivalent efficiency. If yes, he posited that a mutant rVSV(MΔ51)-M3 with wild-type matrix function would have the potential of being more virulent than VSV in humans. Dr. Cattaneo then asked about the probability of such a "revertant" being generated and having the potential of starting a pandemic. The investigators characterized only 6 of the 30 differences between the sequence of rVSV(MΔ51)-M3 and the sequence of the VSV-Indiana strain ("GenBank J02428"); he asked about the origin of the other mutations.

C. RAC Discussion

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

Dr. Cattaneo questioned the investigators' statement that the VSV-New Jersey strain is more virulent and that the VSV-Indiana strain is more attenuated. Although these two viruses are serologically different, both were derived from outbreaks in cattle, and the relevance of virulence vs. attenuation in cattle is unknown in humans.

Dr. Federoff suggested establishing a more robust way of delineating which tumors might be most responsive before commencing the trial.

Dr. Kodish asked whether there is a compelling reason not to use participants who have not progressed.

Dr. Zaia wondered whether, absent tumor, the investigators could look at the dose response of the modified VSV in an intrahepatically delivered nonhuman primate to determine whether the MTD in the primate is similar to what is predicted based on the rat experiments.

Noting the existence of many studies on the effects on tumors of shutting off arterial blood flow, Dr. Kirchhoff asked whether the investigators had used a control group in which rats with tumors had their hepatic arteries clamped without VSV infusion to look for a possible positive effect on the animals due to the clamping alone.

Dr. Federoff suggested using a small number of nonhuman primates as a guide to potential safety issues in humans, since the rat MTD data may not extrapolate to humans and the vascular anatomy of the liver in the rat may differ from that in the human.

D. Investigator Response

1. Written Responses to RAC Reviews

Regarding potential use of this experimental treatment in treatment-naive participants, the investigators explained that the eligibility and exclusion criteria do allow for participation by individuals who have had prior systemic therapy as well as those who had not received prior treatment. On the basis of the findings that median survival was significantly longer with the use of sorafenib, potential participants with HCC will be offered treatment with sorafenib and then will be offered enrollment in this clinical trial at the time of disease progression or intolerability of side effects. Individuals who do not want to be treated with sorafenib also will be considered for participation in this trial.

At the request to Dr. Zaia, the investigators agreed to modify the clinical trial protocol to exclude individuals with preexisting antibody to VSV.

The investigators offered to develop a VSV replication and cell-killing assay to be performed on peripheral blood mononuclear cells (PBMCs) of potential study participants. This assay will help identify prospective participants who are at increased risk for susceptibility to VSV infection.

The investigators agreed to perform *in vitro* studies to test fluoroquinolone and other antibiotics that might be used in participants in this protocol at the time of virus injection to ensure that they do not affect VSV infectivity and replication. If these studies indicate that fluoroquinolones and other antibiotics used in this trial affect VSV infectivity and replication, the investigators will replace them with other antibiotics shown not to affect VSV infectivity.

Serum neutralizing antibody assays against VSV will be performed to assess the immune response of the participant to VSV infection. Detection of serum neutralizing antibody assays against VSV will be important in toxicity assessment as well as for subsequent clinical trials that may use repeated doses of the study virus.

The plan for managing Dr. Woo's conflict of interest includes that he will have no role in participant enrollment and no direct contact with prospective participants, he will have no role in safety data interpretation and assessment of AEs, and he will be excluded from DSMB meetings.

At the suggestion of Dr. Zaia, the investigators will include in the protocol and informed consent document descriptions of the risks and treatment of tumor lysis and the potential disease-causing effects of the recombinant VSV vector. They also will include a statement to indicate that, at certain times during the study, such as immediately after virus injection, participants would need to stay in their rooms because of the potential risk for spreading the virus; blood, urine, and nasal swabs will need to be negative for VSV prior to participant release from the clinical center.

Results of other research studies indicate that M3 expressed by human HCC cells infected with recombinant VSV vector is able to bind and inhibit a broad spectrum of chemokines naturally produced by virus-infected human HCC cells. Although mutant viruses are sometimes capable of reversion to the wild type by spontaneous correction of the mutation, the recombinant vector in this study contains a deletion of three nucleotides in the gene for the matrix protein that is less likely to revert to the wild type, and the investigators have not detected the revertant. In addition, there is no scientific basis to suspect that rVSV-M3 could be transmitted between humans without arthropod passage.

At the suggestion of Dr. Kahn, the investigators agreed to provide additional details regarding the routine laboratory tests to be performed, which will include blood counts, blood chemistries to check liver and kidney functions, and blood tests to check blood-clotting ability. They also will add in the informed consent document a request for autopsy.

The finding that treatment of human melanoma xenografts with wild-type VSV in nude mice resulted in regression or growth inhibition of the established tumor has been postulated to be due to the fact that IFN-responsive antiviral pathways are defective in many tumors, including those of human origin, and thus VSV can replicate within these cells regardless of IFN treatment. It is not known whether IFN sensitivity in primary human HCC cells is attenuated.

When the investigators proposed to conduct a pharmacology/toxicology study using the VSV vector in normal rhesus monkeys, they were told by the FDA that the rhesus monkey was not a relevant animal model because VSV toxicity had not been demonstrated in that species. Instead, the FDA suggested that the investigators perform an extensive pharmacology/toxicology study in normal rats, where toxicity had been established.

Although only a relatively small fraction of the population has been exposed to VSV, the investigators agreed to list the presence of preexisting antibodies to VSV as an exclusion criterion for this protocol.

The investigators stated that they had not performed experiments to test for modulation of the immune response to other infectious agents during dosing with rVSV(MΔ51)-M3; however, they agreed that this important experiment should be conducted.

After the additional animal studies have been completed and before the clinical trial is initiated, the investigators pledged to update the informed consent document and to add a description of the side effects noted in the animal studies.

According to the literature, M3 selectively binds hIL-8, MCP-1, and RANTES, all three of which are important for inducing inflammation. M3 functional activity was demonstrated using conditioned medium from the human hepatoma cell line, Hep3B, infected with rVSV(MΔ51)-M3 and two control vectors. The results indicated that M3 expressed by human hepatoma cells infected with the recombinant VSV vector is able to bind and inhibit a broad spectrum of chemokines naturally produced by virus-infected human hepatoma cells.

Although mutant viruses are sometimes capable of reversion to wild-type by spontaneous correction of the mutation, the recombinant vector, rVSV(MΔ51)-M3 contains a deletion of three nucleotides in the

gene for the matrix protein that is much less likely to revert to wild-type. Should rVSV-M3 be generated by reversion, virally expressed M3 will allow the vector to evade the initial inflammatory cell response to the virus, but not protect the virus from interferon response in normal cells and other aspects of the host immune responses including neutralizing antibodies and virusspecific T cells. There is no scientific basis to suspect that rVSV-M3 could be readily transmitted between humans without arthropod passage.

2. Responses to RAC Discussion Questions

Regarding preliminary data on toxicity of the vector in nontumor-bearing rats, a threefold dose above the MTD led to the death of four out of seven rats. Dr. Woo explained that those deaths were most likely the result of a cytokine storm that led to proinflammatory syndrome and then to multiorgan failure. Therefore, the control of cytokine levels will be critically important in the proposed clinical trial.

Dr. Woo stated that the investigators would discuss with their interventional radiologist the use of a balloon catheter to produce a temporary blockade of the common hepatic artery, since the virus is infused into the gastroduodenal artery, to prevent retrograde throwback to the common hepatic artery. A similar procedure was used in the preclinical experiments.

Dr. Sung reiterated that prospective participants would be presented with all treatment alternatives before they decide to enroll in this Phase I study.

Because of a conflict of interest, Dr. Woo explained that he would have no role in participant enrollment and no direct contact with prospective trial participants. In addition, he will have no role in safety data interpretation or assessment of AEs, and he will be excluded from all DSMB meetings.

Dr. Woo noted that he and his colleagues are appearing at this RAC meeting relatively early in the clinical trial proposal process because they want the RAC's input in the experimental design and the safety and pharmacology/toxicology studies, which have not yet been conducted. If the RAC agrees in principle with the investigators' proposed studies, the studies will be conducted, and the results will be included in the informed consent document.

Dr. Woo explained that the investigators do not know what makes the underlying mutation, in HCC or other tumors, susceptible to VSV; they do know that the IFN response pathway is attenuated in most tumor cells. More than 80 percent of the National Cancer Institute panel of approximately 60 human tumor cells is susceptible to VSV infection and oncolysis.

Regarding testing to determine which tumors might be most responsive to VSV, Dr. Woo stated that such an approach would be appropriate for future efficacy trials. For this Phase I toxicity study, the investigators believe they should test the safety of this approach and then incorporate molecular fingerprinting assays if and when Phase III trials are planned.

Dr. Sung explained that the investigators are willing to enroll patients who have progressed as part of the target population, but they do not want to exclude potential participants who do not want to try sorafinib, an antiangiogenic agent that is the first drug approved by the FDA for treating hepatocellular carcinoma. Dr. Woo stated further that if the RAC requests that the investigators change the protocol so that participants must have evidence of progression before they can be included, they would incorporate that criterion into this protocol.

Dr. Woo explained that some vaccine studies of VSV in rhesus monkeys have used the MTD, but typically those studies have been conducted via the intramuscular (IM) route; no such studies using intrahepatic (intravenous [IV]) infusion have been found in the literature.

Dr. Woo noted that the experimental model for this Phase I trial does not include testing for any difference in efficacy or toxicity with or without clamping of the hepatic artery. However, the investigators are looking at combining virus with embolization, but those experiments are ongoing, and the data are not yet available. Dr. Sung explained further that, in the human liver, the vascular anatomy is such that clamping

of the hepatic artery will not result in the appropriate embolization; the only way to do that would be to conduct a total arterial venous isolation of the liver.

Regarding conducting experiments in nonhuman primates to reiterate the potential MTD in humans, Dr. Woo stated that the investigators are not opposed to conducting such a study in a limited number of rhesus macaques. That study would need to be designed carefully in consultation with the FDA, especially regarding endpoints.

Dr. Woo agreed to include in the informed consent document revised wording about when participants could withdraw from this study. The wording would explain the steps that might be taken to ensure public health if a participant withdrew directly after virus injection.

E. Public Comment

Dr. Borror suggested that the radiation risks on page 10 of the informed consent document, which are listed as "relatively small," should be described more accurately. In addition, she noted some complex language that should be simplified.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

VSV is exquisitely sensitive to type 1 IFNs, and its replication in normal cells is suppressed by a robust type 1 IFN response. It is thought that this IFN response is attenuated in most cancer cells, thus making replication of VSV tumor selective. Given the extent of tumor cell heterogeneity in terms of IFN response and susceptibility to VSV, it would be prudent to develop a way to analyze the molecular signature of each participant's tumor to identify the tumors that are likely to respond to the virus, so that in future studies only those participants would be targeted with the VSV construct. This step would also further elucidate the biological basis for the selective oncolytic property of the VSV construct.

To enhance confidence that this replication-competent virus will not revert to the wildtype virus, additional safety studies should be conducted. These should be designed to establish that reversions to the wild-type phenotype do not occur in either tissue culture or an appropriate murine model. Serial passages of the virus under stress will help establish whether the MΔ51 deletion, which makes the virus less pathogenic, is lost or triggers compensatory mutations at a second site that might affect the virus' phenotype. Such testing should be done with a highly sensitive assay (e.g., polymerase chain reaction).

Toxicology studies in animal models (normal and tumor-bearing rats) have demonstrated a relatively small therapeutic window between a biologically active dose and the MTD, making the margin of error extremely narrow (a significant number of deaths were observed in the toxicology studies in normal rats). The RAC believed that, because of potential biologic differences in humans (e.g., potency of the innate response to VSV or possible limitations in the ability of the rat experience to adequately predict future toxic effects in humans), additional toxicologic studies are needed. To gather more data on this safety issue, it would be helpful to carry out additional toxicology studies in a larger animal model. Moreover, the animal model should be normal, not tumor bearing, and its vascular anatomy should be more similar to the human vasculature than is the rat model. This is necessary because hepatic artery delivery is the planned route of administration in the clinical study, and that route was not used in the rat studies. In addition, hepatic artery ligation was used in the rat studies but will not be used in the clinical trial. Such data also would allow for a better understanding of the expected multiplicity of infection that is expected to occur in normal hepatocytes and whether this level of VSV infection could overwhelm

the endogenous IFN response pathway that will be necessary to inhibit virus replication in normal cells.

Since the insertion of a gene encoding a viral chemokine-binding protein (M3) will suppress neutrophil and NK cell accumulation and will downregulate the innate immune response, animal studies should be conducted to test whether downregulation could affect a participant's ability to respond to other infectious agents during treatment with rVSV(MΔ51)-M3. These studies should be performed with human infectious agents that are primarily controlled by the innate immune system and with liver specific agents, such as hepatitis B and C viruses.

Clinical/Trial Design Issues

Given that this is a Phase I trial assessing safety and that no benefits to participants are expected, enrollment should be limited to individuals who have either failed or refused standard therapy.

Genotypic variations in the innate immune function alter an individual's ability to contain and clear infections. For example, there is an association between the killer-immunoglobulin-like receptor genotype and response to other ribonucleic acid (RNA) viral infections (e.g., HIV and hepatitis C virus). Genotypic variations may lead to increased or decreased susceptibility to the virus and may affect the product's safety and efficacy. Addressing this issue by developing an assay to measure VSV replication and cell-killing rates in PBMCs would be an appropriate proxy for addressing these genetic variations. However, a normative range for susceptibility of PBMCs to the gene-modified VSV will need to be established before the assay can be used to formulate appropriate inclusion/exclusion criteria.

Ethical/Legal/Social Issues

The informed consent document should be revised in the following ways:

The statement that a participant can immediately withdraw from the study at any time is problematic because the protocol, as a public health precaution, requires all participants to remain in isolation in a private room with a private bathroom for approximately 1 week after dosing or until it is established that no virus is present in the blood, in secretions, or in any vesicles that may develop. This mandatory isolation applies to participants who withdraw as well as those who complete the study. As such, it would be prudent to delete "immediately" and to clarify that, although they are free to withdraw at any point, participants will still be required to remain in isolation. The document also should discuss whether participants who decline to remain in isolation would be quarantined in the interest of public health.

The discussion of "Radiation Risks Associated with Scan and X-Rays" is inadequate. It should be revised to enable participants to assess the risks of the proposed radiation exposure. One approach, for example, would be to compare the level of risk of the radiation to the risk associated with background radiation.

Technical terms and ambiguous references, including "genetically modified virus," "advancing the catheter into the artery," "volume of contrast," and "services rendered," should be simplified or clarified.

G. Committee Motion 1

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Ms. Shapiro moved and Dr. Somia seconded the motion that the RAC approve these summarized recommendations. The vote was 15 in favor, 0 opposed, 0 abstentions, and 1 recusal.

IV. Discussion of Human Gene Transfer Protocol #0807-930: A Double-Blind, Placebo-Controlled (Sham Surgery), Randomized, Multicenter Study Evaluating CERE-110 Gene Delivery in Subjects with Mild to Moderate Alzheimer's Disease

Principal Investigator:	Paul S. Aisen, M.D., University of California, San Diego (UCSD)
Additional Presenters:	David Barba, M.D., UCSD *(via teleconference)*; Raymond T. Bartus, Ph.D., Ceregene, Inc.; Andrea Loewen-Rodriguez, Ceregene, Inc.; Jeffrey M. Ostrove, Ph.D., Ceregene, Inc.; Joao Siffert, M.D., Ceregene, Inc.
Sponsor:	Ceregene, Inc.
RAC Reviewers:	Ms. Shapiro, Dr. Strome, and Dr. Williams
Ad hoc Reviewer:	Bradley T. Hyman M.D., Ph.D., Harvard Medical School/Massachusetts General Hospital

Drs. Federoff and Shah recused themselves from consideration and discussion of this protocol due to conflicts of interest. As a result of Dr. Federoff's recusal, Dr. Strome temporarily chaired the RAC meeting for the discussion of this protocol.

A. Protocol Summary

Alzheimer's disease (AD) is the most common cause of dementia, afflicting approximately 4.5 million individuals in the United States. Current standard-of-care (SOC) medications for AD—cholinesterase inhibitors—alleviate symptoms by augmenting cholinergic function; however, they do not prevent the death of cholinergic neurons. Although it has been recognized for almost 20 years that neurotrophic proteins such as nerve growth factor (NGF) can improve function and prevent the death of cholinergic neurons in experimental animals, a practical and safe method for delivering NGF to these neurons in humans has been lacking.

CERE-110 is a genetically engineered, adeno-associated virus (AAV) serotype 2 with modified DNA that expresses NGF protein. Nonclinical research has established that CERE-110 efficiently transfers the NGF gene to the cholinergic neurons in the basal forebrain structure known as the nucleus basalis of Meynert. Evaluation of CERE-110 in humans with AD was initiated in the United States in 2004 in a Phase I feasibility study. The potential clinical benefits demonstrated in animals, the apparent increase in brain metabolism in positron emission tomography (PET) scans of the brain in research participants who took part in the Phase I study, and the acceptable health risk profile of this approach (delivering CERE-110 bilaterally into the brain) support testing CERE-110 in a larger, randomized double-blind study. Safety data from a similar gene transfer product, CERE-120, further support the overall safety of the CERE-110 gene transfer approach.

The primary objectives of this proposed controlled Phase II trial are to evaluate the cognitive effects and safety of CERE-110 administration in research participants with AD. Other objectives include assessing the magnitude of the potential benefits of CERE-110 and assessing a variety of other clinical measures of cognition and daily function. The study also will help assess the feasibility of conducting a trial in multiple U.S. centers with expertise in this type of surgery. PET scans of the brain also will be evaluated as a potential marker of the effects of NGF activity in the brain. Potential research participants will include women and men between the ages of 55 and 80 years who have a diagnosis of mild to moderate AD, who are able to understand the nature of this investigational study, and who can provide informed consent. Participants in the control arm will be eligible to enter a "rollover," open-label study of CERE-110 after the Phase II study is completed, assuming the results support safety and potential efficacy.

B. Written Reviews by RAC Members

Nine RAC members voted for in-depth review and public discussion of the protocol. Key issues included the ethical concerns raised by enrolling participants with impaired cognitive abilities, especially when half of the participants will undergo a sham surgical procedure.

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

Regarding capacity to consent, Ms. Shapiro stated that the significant risks and concerns related to the risk-benefit balance for control-arm participants highlight the need for careful determination of the capacity to consent, and because this study will last for more than 2 years, it is possible that participants will lose the capacity to provide informed consent prior to the study's conclusion. She raised serious ethical concerns about the imbalance between risks to participants in the placebo group vs. potential benefits to them and to society and the notion that sham surgery violates the ethical and regulatory principle that the risk of harm to participants must be minimized. Ms. Shapiro requested that the investigators comment further on the need to evaluate the placebo effect for this participant population, on the risk-benefit balance, and on alternative research designs that would pose lower risks of harm. With regard to the informed consent document, she stated that portions of the document are written in an overly optimistic fashion, the consent for storage and future use of blood samples is unclear, the discussion of AD drug treatment in the "Alteratives" section is repetitive and unclear, and the "Benefits" section should be modified to state clearly that, although CERE-110 may have some benefit, that benefit is not available to the 50 percent of participants who will be enrolled in the control arm. Ms. Shapiro asked the investigators to explain why a legally authorized representative (LAR) and a legal guardian are included in the informed consent document, when the inclusion criteria include the capacity to provide informed consent.

Dr. Strome asked about evidence of cognitive improvement in the Phase I trial, whether immune response to AAV would be measured in the current study, whether other tests such as liver function tests would be performed (especially in light of toxicities with other AAV studies), and how the transgene would be measured and how the investigators would interpret the results of a negative study if no direct measurement is intended. He suggested that the power calculation might result in an underpowered study for detecting a meaningful response and, as such, asked whether the investigators plan to expand the number of participants on the basis of interim data. Dr. Strome expressed concern regarding appropriate informed consent in this vulnerable participant population and asked the investigators to define any potential conflicts of interest and state whether a treating physician could recruit a participant and/or administer informed consent. Noting that there appears to be no method for making a partial burr hole, he asked the investigators to describe what would occur in the case of accidental dural exposure or laceration in a participant in the control arm of this study.

Dr. Williams asked the investigators to clarify how they would determine the competence of the research participants to enroll in this study.

Noting that recent AD trials have failed without having biomarkers to determine whether primary biochemical goals had been achieved, Dr. Hyman asked what positive control might be incorporated into the design of this trial to act as a positive biomarker for successful NGF transduction. He noted that monitoring for anti-NGF and anti-AAV antibodies is proposed and asked what actions would be taken if those antibodies were detected. Earlier studies in Sweden using intraventricular NGF led to marked side effects in three participants who experienced pain and weight loss; given that the AAV in this trial is designed for long-term NGF production and cannot be turned off, Dr. Hyman asked the investigators what actions they would take if side effects similar to those in the Swedish trial were to occur. Because participants may progress beyond entry criteria or might no longer be competent to consent during the 25+ months of this trial, research advance directives should be considered for inclusion, and wording about what would occur in that eventuality should be presented in the informed consent document. Dr. Hyman noted that the sham procedure might raise concerns about being "more than a minor increment above minimal risk" for local review boards and does not meet Alzheimer's Association guidelines for

being likely to yield generalizable knowledge about a participant's condition. He urged the investigators to reconsider control-group procedures that do not lead to more than a minor increment above minimal risk.

C. RAC Discussion

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

Dr. Zaia asked whether the study partner would be the caregiver.

Ms. Shapiro asked for clarification about the kind of consent the investigators hope to obtain from the study partner.

If a determination is made that placebo sham surgery is an appropriate trial design, Dr. Kodish recommended that the investigators consider asking each potential participant to write in his or her own words, "I understand that there is a 50/50 chance that I will receive the sham surgery"—an ethically meaningful procedure to ensure that participants understand how the trial design might impact them.

Dr. Strome asked whether the study is powered appropriately to detect a 50-percent improvement in function.

Dr. Strome suggested that the investigators consider redesigning this study to enroll additional participants such that the currently described primary analysis becomes an interim analysis that could continue if results are positive.

Dr. Wei wondered whether the absence of AEs in the Phase I trial means that the dose was too low.

Ms. Shapiro recommended that the investigators retain their decisionmaking capacity analysis. Study partners, a required part of this trial, should acknowledge that they have a role and that they agree to fulfill this role; the study partner should not consent on behalf of the research participant. Study partners also should acknowledge that, in the future, they may be asked to fulfill the role of the LAR, which will mean being asked to take over decisionmaking capacity for the research participant with regard to this clinical trial.

Dr. Strome asked whether there have been other AD studies that had shown 50-percent changes in cognition with a small number of research participants.

Several RAC members commented on the need to minimize control-arm risk by changing or reducing the need for general anesthesia.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators agreed with Ms. Shapiro that the ethics of including a control group in which individuals with AD undergo a sham surgical procedure after placement of a stereotactic frame and under general anesthesia deserves careful consideration. However, given the safety data obtained for CERE-110, the dismal therapeutic options available, and the potential of the treatment under investigation, the risk-benefit ratio for this intervention is deemed justified, and the use of a sham-surgery control is ethically justified and warranted.

Capacity to provide consent will be assessed by the site investigator, guided by a version of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) questionnaire adapted

specifically for this trial. Though enrollment will be limited to those participants assessed to have capacity to consent, for each participant consent will also be obtained from a LAR.

As to whether other study designs or choice of control group could obviate the need for using a sham-surgery control, the investigators stated that rigorous blinding through employing a control group undergoing sham surgery and other measures of blinding are critical for the ethics of this study; a matched control (open label) would not address the potential bias and would weaken study conclusions.

In clinical trials enrolling cognitively impaired individuals, it has become common to obtain consent from both the research participant and the LAR. Although this trial will include an assessment of a participant's capacity to consent, such an assessment is subjective, and the investigators stated their belief that consent from the LAR is also required. Capacity to consent and assent to study procedures may decline with time; consent from the LAR is essential in such instances. The LAR is often the study partner (typically the spouse or adult child), who is an active participant in the trial and its outcome measures and therefore must provide consent. If the LAR and the study partner are not the same individual, the investigators will require both to sign.

Regarding measuring transgene expression, currently, there are no means to directly measure the expression of the transgene in vivo. A retrospective assessment of transgene expression is possible by analysis of post mortem brain tissue. This may include analysis of NGF protein expression by immunohistochemistry and/or analysis of NGF mRNA expression by in situ hybridization on histological brain sections. Nonhuman primate, as well as rodent, studies indicate that it is possible to control transgene expression by changing the dose of vector genomes administered; the greater number of vector genomes administered, the wider the spread of protein within the brain and the higher the protein expression.

Subjects undergoing the sham surgical procedure in this controlled Phase 2 study will undergo a partial burr hole using the same procedure successfully employed in the CERE-120-02 (AAV2-NTN) Phase 2 Study (OBA #0607-788). In the CERE-120-02 Phase 2 study (N=58, randomization ratio 2:1, active: control), sham surgical procedures were conducted safely and there were no instances where the dura was breached. The burr holes for this proposed trial are made with a high speed hand drill, not the older style clutch drill system. This high speed drill allows the surgeon to make a cranial opening specially tailored to accommodate the trajectory for the three intracranial targets in the group receiving CERE-110. For subjects undergoing sham surgery, this high speed drill system makes it very easy to limit the depth of the bone opening to include only the outer table of the skull (approximately 5-10 mm). In the highly unlikely event of a dural opening during the procedure, the dural tear would be closed with fibrin glue after good hemostasis is achieved.

Data from the previous trials reinforce the overall safety of CERE-110 administration but no efficacy conclusion can be drawn. Brain FDG-PET scans performed at baseline, 6, 12 and 24 months suggest an increase in metabolic activity, compared with baseline, in areas related to the cholinergic circuitry. These findings were further corroborated by a comparison of the FDG-PET images with historic controls of untreated AD patients followed prospectively for 6 months. Similar findings were also reported for six subjects with early stage AD in an *ex vivo* NGF gene study with implants of autologous fibroblasts genetically modified to produce NGF into the brain parenchyma at the dorsal perimeter of the NBM. The small sample size precludes any conclusions on the metabolic effects of CERE-110 at this stage.

2. Responses to RAC Discussion Questions

Dr. Siffert explained that none of the 10 participants who have received CERE-110 has experienced either weight loss or pain, and there have been no side effects that the investigators could ascribe to CERE-110. Likewise, in the CERE-120 program (a separate program that is administering growth factor directly into the brain), there have been no AEs that were parallel to the AEs seen with IV injection. These participants were dosed approximately 30 months ago in the Phase I Parkinson's trial. The additional cohort of approximately 40 participants shows no evidence of either weight loss or pain. If

these AEs were to occur and because there are no means to turn off NGF production, management would be symptomatic for pain and nutritional support for weight loss.

Dr. Aisen explained that, in this clinical trial, the investigators feel an obligation to provide whatever service possible to the participants, which means open-label exposure to active treatment even though the open-label dosing may not have been adequately or at all shown to be effective. They intend to offer open-label "treatment" to the placebo group and to the active-dose group, from the close of the protocol until the analysis is finished; however, it will not be possible to weigh benefits vs. risks of this addition to the protocol.

Dr. Aisen acknowledged that the investigators would not be able to distinguish, with any confidence, (1) a negative trial resulting from failure to deliver to the correct area and/or delivery of a suboptimal dose from (2) the conclusion that NGF does not work. There does not exist any direct measure in a living person of NGF expression in the nucleus basilis that would allow the investigators to confirm that the biological pharmacodynamic effect was reached. However, they do hope to be able to evaluate brain tissue in participants who have died.

Regarding an adaptive design that would allow the investigators to augment the number of participants to achieve a statistical result, Dr. Aisen explained that the investigators have considered this question and have not come up with such a design; in addition, the current trial is too small to allow a useful interim adaptive analysis. The study is designed to have 80-percent power to demonstrate a 50-percent slowing of cognitive decline. Although a 50-percent slowing is within the realm of possibility, a 25-percent slowing would not demonstrate a clinically important effect on cognition.

For an AD therapy to succeed, Dr. Aisen pointed out the need to demonstrate a signal on a cognitive measure and a clinical measure. Clinical measures are based on information from study partners that would not be useful from an unblinded study partner. Thus, there appears to be no alternative to a concurrent blinded control group, and the investigators believe that that blind requires a sham surgery and that they are proposing the safest possible blinded sham surgery.

To ensure an understanding of a simplified version of the trial, Dr. Aisen explained that individual participants must understand that they do not have to participate, that this clinical trial is research, that they have a 50 percent likelihood of getting a sham surgery, that the sham surgery cannot provide any benefit, and that they may never have an opportunity to get active treatment. There is likely to be substantial uncertainty regarding the judgment of the participant, so it is standard practice in AD therapeutic trials to obtain dual consent to include the LAR who, in 90 percent of AD trials, is also the study partner.

After considerable discussion, Dr. Aisen agreed to change the trial design to require consent from the participants after the capacity assessment and from the study partner who must be an active participant. If the study partner is not the LAR, the investigators will not ask the LAR to consent because they have already determined that the participant has adequate capacity to consent.

Dr. Bartus explained that, in the nonhuman primate and rodent studies that led up to the Phase I and the proposed Phase II studies, as well as in the CERE-120 Parkinson's program, the investigators did not see a single toxic event in any animal, in any tissue, at any dose, or at any timepoint, despite the fact that the dose multiples in the preclinical Parkinson's program were 100 and 400 times higher than the initial dose given to humans in the clinical trial. The reason for that lack of AEs is because of the biology of growth factors—if the growth factor remains targeted in a controlled fashion to the neurons that require trophic-factor support, the biological consequences are innocuous at worst and therapeutic at best. This result is consistent with the human experience with growth factors.

The study partner is the person who accompanies the participant to visits and is the informant on those measures that require an informant. Dr. Aisen explained that most often that person could be described as the caregiver—a spouse or an adult child in close contact with the research participant.

Regarding the sham-surgery procedure, Dr. Siffert explained that the higher risk for the sham procedure is general anesthesia and that the actual skin incision and the partial burr hole represent confined risk. Participants will be assessed carefully prior to being offered participation in this trial to make sure they can withstand general anesthesia safely and will be monitored carefully. The duration of surgery is a critical point of the blinding, because the duration is visible to family members, to the participant, and to nonneurosurgical study staff members. The sham surgery must be indistinguishable from the actual procedure; otherwise, the purpose of putting participants through a sham surgery will be defeated.

Dr. Aisen stated that there have been no positive results in studies of disease modifiers in AD.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Clinical/Trial Design Issues

The study is currently powered to have an 80-percent chance of detecting a 50-percent slowing in cognitive change, which would be a very significant result. However, the study is probably not sufficiently powered to detect meaningful changes below the 50-percent threshold. One way to address this limitation would be to use an adaptive design in a larger initial cohort that would build in an interim efficacy analysis at 50 participants to determine whether a 50-percent difference in efficacy is being detected.

Members of the RAC expressed concern about the decision to include a control arm requiring both a neurosurgical procedure and general anesthesia. A serious complication from general anesthesia is rare, but the risk is not insignificant. The protocol and the informed consent document should include a discussion of why general anesthesia is being used and why an alternative such as conscious sedation cannot be used in the control arm without compromising the blind.

Previous studies with systemic administration of NGF protein led to weight loss and pain syndrome, both of which stopped after the administration of NGF was halted. Because this study employs intracranial administration of a vector that is expected to continually produce the transgene product, NGF production cannot be turned off. If this side effect occurs, only symptom management can address it. The protocol and the informed consent document should discuss this risk and how it will be addressed, including through the use of medication.

Ethical/Legal/Social Issues

The study may allow participants in the placebo arm to receive the active agent in an open-label phase of the study, assuming that safety and efficacy are seen. However, participants in the placebo arm may experience additional cognitive decline over the course of the study so that they are no longer competent to consent at the time a decision is made to offer open-label use. It may be useful to address this issue at the time of enrollment and document the participant's preference. This documentation would serve as guidance to the participant's representative should their involvement become necessary.

The consent process will use a MacCAT-CR to help establish that the research participant has the capacity to consent. However, even when the participant has the capacity to consent, the protocol will require an LAR to sign the informed consent document, which

undermines the participant's autonomy. If the participant has the capacity to consent, an LAR signature is not needed.

In addition, the study partner must acknowledge by signing the informed consent document that he or she has agreed to assist the participant in his or her study participation. It would be preferable to add an acknowledgment to document the study partner's willingness to assume the role of LAR in the event that the research participant is no longer able to consent.

Notwithstanding the use of the MacCAT-CR, because of the ethical considerations of the study design, particularly the use of a sham neurosurgical procedure using general anesthesia, and due to the enrollment of a cognitively impaired study population, it is important to be doubly sure that the participants understand the study procedures and the possibility that they may be in a control group. One approach would to ask the participant to verbalize their understanding of the study design, procedures, and risk-benefit considerations and to consider using an independent person to document this affirmation.

Another measure to ensure the validity of the participant's consent should be taken. The participants' treating physicians should not be involved in the consent process, since they could exert influence about study participation.

The following changes should be made to the informed consent document:

- Clarify whether the study partner and the LAR are the same person, and if not, what their respective roles would be.
- Discuss the risks associated with dura exposure and tearing, no matter how unlikely, and how these injuries would be managed.
- Avoid the term "gene therapy." The argument that the term should be used because it is more commonly used in the lay press is unconvincing. The term perpetuates the therapeutic misconception. The term "gene transfer" should be used instead.
- Clarify the discussion of AD drug treatment in the "Alternatives" section (page 11 of 17), which is repetitive as written.

G. Committee Motion 2

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Dr. Zaia moved and Dr. Yankaskas seconded the motion that the RAC approve these summarized recommendations. The vote was 13 in favor, 0 opposed, 0 abstentions, and 2 recusals.

V. Day 1 Adjournment

Dr. Strome, temporary RAC chair, adjourned Day 1 of the September 9-10, 2008, RAC meeting at 6:10 p.m. on September 9, 2008.

VI. Day 2 Call to Order and Opening Remarks

Dr. Federoff, RAC Chair, opened Day 2 of the September 9-10, 2008, RAC meeting at 8:15 a.m. on September 10, 2008.

VII. Minutes of the June 17-18, 2008, RAC Meeting

RAC Reviewers: Drs. Flint and Somia

Dr. Somia stated that the minutes of the June 17-18, 2008, RAC meeting were thorough and complete and were a good representation of what was discussed at the meeting.

A. Committee Motion 3

Approval of the June 17-18, 2008, RAC meeting minutes was moved by Dr. Kodish and seconded by Dr. Strome. The RAC voted unanimously by voice vote to approve the June 17-18, 2008, RAC meeting minutes.

VIII. Discussion of Human Gene Transfer Protocol #0807-932: A Randomized, Placebo-Controlled, Double-Blind, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of Multiple Intravenous Doses of ANZ-521 in Treatment-Naive Hepatitis C Patients

Principal Investigator:	Eric J. Lawitz, M.D., Alamo Medical Research
Additional Presenters:	Dirk G. Brockstedt, Ph.D., Anza Therapeutics, Inc.; Andrea L. Cox, M.D., Ph.D., Johns Hopkins University; Thomas W. Dubensky, Ph.D., Anza Therapeutics, Inc.; Dung Thai, M.D., Ph.D., Anza Therapeutics, Inc.
Sponsor:	Anza Therapeutics, Inc.
RAC Reviewers:	Drs. Ertl, Kahn, and Wei

A. Protocol Summary

Hepatitis virus type C (HCV) infection is a major cause of morbidity and mortality worldwide. An estimated 170 million individuals are infected with HCV around the world, with nearly 4 million people chronically infected in the United States and up to 9 million people chronically infected in Europe. Of those exposed to HCV, 80 percent become chronically infected, and at least 30 percent of carriers develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. The current SOC for patients in the United States with chronic HCV infection, IFN-alpha (IFN-□) and ribavirin, has been shown to be less than 50 percent effective among individuals with genotype 1 chronic infection, the most prevalent HCV genotype among infected individuals in the United States. The toxicity and tolerability profiles of IFN-□ and ribavirin limit their use in treatment for HCV infection; thus, there is a continued need for effective new therapies.

Anza Therapeutics, Inc. (Anza) has developed an immunotherapy strategy based upon a live-attenuated *Listeria monocytogenes* strain (*Lm* Δ*actA*/Δ*inlB*) that can potentially enable the host's immune system to eliminate the virus in chronically infected individuals via stimulation of an innate and adaptive immune response. A significant barrier to the development of an HCV therapeutic vaccine is that HCV is a highly diverse virus. To address this virus sequence diversity, the ANZ-521 investigational agent encodes a consensus sequence corresponding to portions of the HCV NS5B and NS3 proteins that also includes the incorporation of directed mutations to abrogate any potential activity of the fusion protein. Use of a consensus sequence reduces the number of amino acid differences between the antigen and circulating strains and maximizes the number of epitopes shared by the vaccine sequence and any individual circulating strain, thus increasing the likelihood that vaccine-induced immune responses will be reactive against the specific virus infecting a given individual.

The safety of ANZ-521 is supported by studies in mice showing comparability between ANZ-521 and similarly constructed investigational agents developed by Anza that have been evaluated in extensive nonhuman primate studies and in human clinical trials (ANZ-100 and CRS-207).

Anza proposes to conduct a Phase I randomized, placebo-controlled, multidose escalation followed by a dose-expansion study in adult participants who have chronic genotype 1 HCV infection and compensated liver disease and who have not received prior treatment with IFN-□ and ribavirin. This Phase I clinical study will consist of three parts. In Part A, each of 3 dose cohorts will consist of 4 participants (3 receiving ANZ-521 and 1 receiving saline placebo) dosed intravenously every 3 weeks for a total of 3 doses. In Part B, participants will be randomized to receive ANZ-521 (12 participants) or placebo (12 participants) at a dose up to the MTD as determined in Part A. In Part C, placebo participants in Parts A and B may be given the option to receive active treatment based on safety and efficacy data. Safety parameters to be assessed include AEs and clinical laboratory tests. Efficacy parameters include immune monitoring and measurements of HCV levels in the blood to evaluate the possible therapeutic benefit of the ANZ-521 investigational agent.

B. Written Reviews by RAC Members

Nine RAC members voted for in-depth review and public discussion of the protocol. Key issues included the novelty of the approach for this disease in patients, who are particularly vulnerable given their clinical condition.

Three RAC members provided written reviews of this proposed Phase I trial. Dr. Federoff summarized Dr. Kahn's review at this meeting because Dr. Kahn was unable to attend.

Acknowledging that standard treatment for HCV infection is lengthy and often fails, Dr. Ertl suggested that the plan to conduct this Phase I trial in treatment-naive individuals—rather than in individuals who have exhausted their treatment options—might not be warranted. She noted that the cytokine responses induced by the vaccine are expected to be short lived and thus unlikely to be as effective as the sustained traditional therapy. In addition, Dr. Ertl noted that this proposed trial's focus on therapy-negative individuals implies that efficacy is expected, although Phase I trials are not geared toward proving efficacy. She requested that the investigators reconsider including treatment-naive research participants and discuss the potential for the experimental vaccine's efficacy. Regarding the dose-escalation schema, Dr. Ertl stated that the investigators' proposal to proceed with dose escalation within 7 days after the second dose is too early and that the waiting period between dosing of participants should exceed 24 hours. She requested additional details about the tests that would be used to monitor participants for immunological responses.

Dr. Kahn focused his comments on the selection of research participants and the informed consent document and process. He expressed concern about limiting participation in this clinical trial to treatment-naive individuals, which he indicated would have the effect of denying those participants access to potentially effective therapies, and stated that it would be more ethically justifiable to recruit participants for whom other treatments had failed. In relation to the informed consent document, the investigators should include a statement about the expected lack of therapeutic benefits from this trial and about this trial being the first use of ANZ-521 in humans with HCV infection and should remove references to ANZ-521 providing benefits. Dr. Kahn asked why women participants must be postmenopausal or surgically sterilized rather than required to commit to using birth control.

Dr. Wei stated that he had no objection to the use of a control group as long as no harm to those participants would ensue and stated that the proposed dose-escalation scheme is standard and not at issue in this clinical trial.

C. RAC Discussion

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

> Dr. Zaia asked how much biomarker analysis would be conducted to document participants' differing responses to the investigational agent.

In reference to an adverse event involving hypotension that occurred during another protocol using CRS-207, Dr. Kirchhoff offered several suggestions about how to deal with the possibility of dehydration prior to study participation, including asking potential enrollees a formalized list of questions that could pick out individuals who might be dehydrated and, therefore, might be at higher risk for getting hypotensive with the dosing. Those individuals would not need to be excluded but could be asked to return the following day after drinking significant amounts of water and no alcohol.

Dr. Federoff asked the investigators to discuss their understanding of the mechanism of the transient hypotension experienced in the other Phase I trial and what they are doing mechanistically to help understand that AE.

Dr. Strome asked for additional details regarding how the participant who experienced an AE in the other Phase I trial was treated.

Dr. Federoff asked whether the investigators knew of any biological basis to believe that the MTD of the experimental agent could be different for treatment-failure individuals vs. treatment-naive individuals.

Dr. Ertl asked about the nature of the stopping rules for this protocol compared with the CRS-207 trial.

Dr. Federoff summarized the hypotension-related concerns of RAC members by stating that the investigators should be as conservative as possible regarding safety issues and that the manner in which the hypotension AE was handled clinically was not acceptable.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators explained that the low level and transient presence of ANZ-521 in the brain of mice in preclinical experiments are consistent with previous animal studies conducted with ANZ-100 and CRS-207, both of which have been evaluated subsequently for their safety and tolerability in Phase I trials in research participants with advanced solid cancers.

The proposed trial with ANZ-521 is designed as a Phase I/II proof-of-concept study to provide both safety and efficacy data that will allow more definitive decisionmaking for additional studies of *Lm* encoding HCV antigens as an immunotherapeutic in a monotherapy setting. Ideally, efficacy testing would be conducted in a treatment-naive population, and the confidence of the decision to proceed is based on selection of the appropriate participant population. Evidence exists that patients who fail prior SOC treatment (combination IFN-□ and ribavirin) are more likely not to respond to an immunotherapy given as a single agent. In a treatment-failure population, the decision to proceed could not be made reliably until a combination trial with other agents was conducted, which could result in unnecessary participant exposure.

The investigators stated that they are not aware of any literature that correlates immune responses in mice to clinical responses in humans in the setting of HCV. However, ANZ-521 elicited a variety of innate and adaptive immune effectors that are known correlates of resolution of HCV infection in humans. The cytokine response is short lived relative to the dosing interval, but the investigators also have measured NK cell activation that might lead to clearance of HCV-infected hepatocytes on an extended timeframe.

The AE profile for the live-attenuated *Lm* platform up to $1x10^9$ colony-forming units (cfu) has been limited to fever responsive to antipyretics and transient hypophosphatemia, lymphopenia, and hemodynamic changes. These events did not result in significant adverse clinical consequences. No cumulative clinical toxicities have resulted from multiple dosing of CRS-207; effects of CRS-207 on body temperature, serum

phosphate, lymphocyte count, and vital signs have not been more pronounced after the second, third, or fourth dose relative to the first. On the basis of these results, the investigators do not expect cumulative toxicities from repeated administration of ANZ-521.

The length of the observation period prior to dose escalation and the dosing of each participant are based on both the anticipated risk of ANZ-521 and the practicality of conducting a dose-escalation study within a reasonable timeframe. In this study, dose escalation will occur after a formal review of at least 7 days of safety data after the second dose of ANZ-521; regular communication with the PIs and sites will ensure that all significant safety signals are known prior to dosing each participant. The approximate 24-hour time period between dosing each participant in the first cohort was implemented to avoid acute catastrophic events in multiple research participants; clinical trial data at doses a hundredfold higher than the starting dose in this trial suggest that live-attenuated *Lm* is safe and well tolerated and would not be associated with acute catastrophic AEs.

The use of a placebo in this proposed protocol is an essential component of good clinical design. The inclusion of a placebo-controlled group is important for evaluating the safety, tolerability, and efficacy profile in research participants with chronic HCV infection. The use of a placebo control in a blinded setting facilitates a more objective evaluation of AEs and toxicities in the setting of underlying disease, and the use of a control population enables accurate determination of antiviral effects due to ANZ-521, beyond the normal fluctuation in viral titer in the placebo group.

If ANZ-521 is found to be safe and provides some benefit, either by lowering viral titer or decreasing liver transaminase levels, then placebo participants will have the option to receive ANZ-521 in a rollover cohort (Part C). A risk-benefit analysis will be conducted after reviewing clinical data from Part A and Part B to determine whether the study should continue. If there is no clear decrease in viral titer or improvement in hepatic transaminase levels even with demonstrated safety and tolerability from Part A and Part B, then placebo participants would not be rolled over to Part C.

2. Responses to RAC Discussion Questions

Dr. Cox, a practicing HCV clinician at Johns Hopkins University, admitted that HCV is a challenging virus. In its thousands of years of presence in human beings, HCV has learned to evade the human immune system remarkably well, as evidenced by the fact that the majority of infected individuals fail to clear this infection. The SOC for HCV is pegylated IFN, a nonspecific immunomodulatory agent. Although it is true that treatment with pegylated IFN produces a 50-percent response rate, the vast majority of people with HCV infection never get treated because more than 70 percent of patients with chronic HCV are not eligible for this therapy. All the current new therapies are being tested with a nonspecific immunomodulatory agent; replacing a nonspecific immunomodulatory agent with an agent that could specifically channel the immune response and direct it against HCV infection potentially could improve the SOC dramatically.

Regarding enrolling treatment-naive participants, Dr. Thai noted that the FDA's Antiviral Drugs Advisory Committee (ADAC) states that treatment-naive participants can be enrolled in these kinds of studies because the SOC is not ideal. He further suggested that, if the investigators enroll only treatment-failure participants, they would not be able to make confident decisions about whether to proceed to Phase II, because a negative signal in a treatment-failure patient could be caused by the investigational agent or could be the result of the specific characteristics of the selected participant population.

Because it is possible that, due to the younger age of this participant population, the cytokine response might be more exaggerated than expected, Dr. Thai explained that the investigators plan to dose at least a hundred fold below the highest dose that has been well tolerated in other trials ($1x10^9$ cfu), and the doses would be modified if a pronounced cytokine effect is observed at $1x10^7$ cfu.

With regard to dose escalation and dose expansion, concerns were raised by RAC members and in discussions with the FDA about enrolling treatment-naive participants. Dr. Thai explained that the investigators, therefore, have changed the enrollment criteria so that treatment-failure participants will be

enrolled in Part A, which will generate the initial safety database and respond to the expressed ethical concerns. They will then enroll treatment-naive participants in Part B to obtain an efficacy readout, with the goal at the end of Part B of making confident decisions about the presence of any clinical signal of viral titer reduction that would warrant additional studies. Part A results will establish the safety and tolerability issues and will establish the MTD; all Part B participants will receive that MTD, so no dose escalation will occur.

Dr. Thai confirmed that the investigators are not aware of any significant differences that would affect the risk profile of a treatment-failure individual versus a treatment-naive individual.

Regarding the AE of blood pressure drop in clinical trials of similar investigational agents, Dr. Thai explained that the clinically significant hypotension effects were seen at a dose of $1x10^{10}$ cfu and that the investigators do not plan to use that dose in this trial. At a dose of $1x10^{9}$ cfu, one participant's systolic blood pressure dropped to the high 80s from the low 100s, and prior to that dosing the investigator had noted that the participant was dehydrated. All of the subsequent participants enrolled in that trial have received some postdose hydration, which has prevented any blood pressure changes. In addition, the investigators for this trial plan to be selective about what kinds of medications are continued prior to dosing.

Dr. Thai offered to restructure the protocol to address the question of whether treatment-naive and treatment-failure participants would respond differently in terms of safety. Once the investigators have established the MTD in the treatment-failure group, they could dose a limited number of participants in the Part B treatment-naive group, get a sense of whether that MTD is safe in this participant group, and then continue for the rest of the trial. This method would demonstrate response comparability between the participants in Part A and those in Part B.

Dr. Thai explained that the placebo enrollment serves two purposes—to benchmark safety and to benchmark efficacy. Guidelines from the American Association for the Study of Liver Diseases and the FDA's ADAC acknowledge that use of placebo is acceptable in this setting provided that the participant has compensated liver disease, does not have advanced fibrosis, and has a low likelihood of progression.

Because they do not have a good understanding of the effects on pregnancy of live attenuated *Lm*, the investigators have decided to limit enrollment to participants who are sterile.

To address concerns about participants being dehydrated prior to dosing, Dr. Thai suggested that the quickest and simplest first screening for blood pressure concerns would be for the investigators to screen participants for significant orthostasis that would indicate dehydration.

Dr. Thai explained the chronology the hypotension AE experienced by one participant in a clinical trial of CRS-207. The first hypotensive episode was a transient systolic reading of 83 after the second of three infusions. The participant was asymptomatic and responded to IV fluids with a systolic blood pressure reading that rebounded to the 110s range during the ensuing 30 minutes, a result that was not significantly different from what was seen previously in other participants dosed at $1x10^{9}$ cfu. At this point, the investigator elected to continue the third and last dose to complete the infusion.
Dr. Thai clarified that, in this protocol, any clinically significant effect will trigger the end of dosing.

E. Public Comment

No public comment was offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Clinical/Trial Design Issues

The vector is designed to institute a T-cell-mediated response against hepatocytes infected with HCV. A T-cell-mediated response may have a therapeutic effect, but a robust adaptive cellular immune response can lead to hepatotoxicity that may not become clinically apparent for up to 2 weeks and also may be more pronounced after booster immunizations. Therefore, dose escalation to the next dose cohort should not occur until 2 weeks after at least one participant has received all three doses in the lower dose cohort. In addition, there should be 14 days between the first participant dosed and the second participant dosed within the same cohort.

The protocol has been modified in response to the RAC review so that only those participants who have failed standard therapy with IFN-α and ribavirin will be enrolled in the dose-escalation phase. Once the MTD is established, the next phase will include additional participants at that MTD. In this phase, participants who are treatment naive will be able to enroll. Since these participants have not received treatment, it is not clear whether they would have been responders or nonresponders. Those who might have responded to standard treatment may potentially have a stronger immune response to the gene transfer vector because of differences in their immunological response to their chronic HCV infection. Although it could result in greater efficacy, it could also raise a safety issue. As such, before expanding the enrollment of treatment-naive participants, it would be prudent for the investigators to test the MTD in several treatment-naive participants to be sure that the MTD is indeed safe in those participants.

There have been several episodes of hypotension in the investigators' ongoing cancer trial using the same live-attenuated *Lm* platform. As such, it would be helpful in this study to try to elucidate the biological mechanism of the adverse reaction; this would provide a better understanding of the safety profile of the vector. In addition, attention should be paid to individual participant characteristics—including medical history, concomitant medications, and testing for orthostatic hypotension—that may elevate their risk for hypotension. Management of participants determined to be at higher risk should be tailored to address their individual risk factors and to minimize the risk of this type of AE.

The protocol should include specific stopping rules in the event that a participant experiences clinically significant hypotension or another adverse reaction during infusion of the study agent. The threshold for stopping the infusion needs to be very low, since this is a Phase I study, and therefore, the participant is not expected to receive direct benefit from the infusion. Criteria to withdraw participants from additional infusions based on these stopping rules should be developed.

The success of this approach, in part, will be a function of the participant's ability to generate an appropriate T-cell response against HCV infection. However, it is known that in patients with chronic viral infections such as HCV, antigen-specific T cells may have impaired function. These cells have been described as "exhausted." The presence of such T cells may limit the effectiveness of the approach. Therefore, PBMCs should be collected prior to and after dosing to allow for additional analysis of the T-cell responses and their correlation with clinical effects.

Ethical/Legal/Social Issues

The informed consent document should be amended to make clear that (1) the study is not expected to provide therapeutic benefits to research participants, and (2) this is the first clinical trial of ANZ-521 for HCV infection (i.e., the vector has never before been used in humans with HCV infection).

G. Committee Motion 4

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Dr. Ertl moved and Dr.Yankaskas seconded the motion that the RAC

approve these summarized recommendations. The vote was 18 in favor, 0 opposed, 0 abstentions, and 0 recusals.

IX. Discussion of Human Gene Transfer Protocol #0807-931: A Phase I/II Trial of Diaphragm Delivery of Recombinant Adeno-Associated Virus Acid Alpha-Glycosidase (rAAV1-CMV-GAA) Gene Vector in Patients with Pompe Disease

Principal Investigator:	Barry J. Byrne, M.D., Ph.D., University of Florida
Additional Presenter:	Cathryn S. Mah, Ph.D., University of Florida *(via teleconference)*
Sponsor:	Powell Gene Therapy Center, University of Florida
RAC Reviewers:	Drs. Bartlett, Kodish, and Yankaskas
Ad hoc Reviewer:	Priya Kishnani, M.D., Duke University Medical Center *(via teleconference)*

A. Protocol Summary

The long-term goal of the proposed research is to develop a gene transfer strategy for Pompe disease (PD), which is an autosomal recessive form of muscular dystrophy (MD) due to glycogen storage. This clinical trial will focus on the respiratory insufficiency and diaphragm weakness that results from mutations in the *GAA* gene encoding acid-□-glucosidase. Currently, there is no cure for PD, and treatment options are severely limited. Therefore, the overall objective of this proposed protocol is to develop a virally mediated gene transfer of *GAA* and to investigate its functional and physiological consequences in *GAA*-affected muscle.

In establishing a clinical program for treating PD using AAV vectors, the first step is to establish the safe and effective delivery of AAV vectors to dystrophic muscle using an approach that is clinically relevant. The specific aims of this protocol are to develop AAV vector constructs expressing human *GAA* for the purpose of characterizing the direct toxicity of these constructs when delivered to the diaphragm as well as to evaluate the potential for long-term carcinogenicity and reproductive toxicity. Research participants will be children with PD who are ventilator dependent despite receiving enzyme replacement therapy (ERT).

Using an established animal model (*GAA*-deficient mouse) in a series of platform studies will support the clinical application of AAV vector delivery to striated muscle in research participants with PD. Aside from its relevance to individuals with PD, this research may offer a therapeutic option to patients who present with other striated muscle diseases.

B. Written Reviews by RAC Members

Nine RAC members voted for in-depth review and public discussion of this protocol. Key issues included the novelty of the approach for this disease in pediatric patients, who are particularly vulnerable given their clinical condition.

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

Regarding potential dissemination of vector beyond the injection sites and the consequences of transgene expression in nonmuscle tissue, Dr. Bartlett asked whether vector biodistribution studies had been performed in an animal model following direct IM injection into the diaphragm, whether the pleural or peritoneal mesothelial membranes are expected to be permeable to vector, and the consequences of hepatic *GAA* expression, given that vector leakage would likely lead to significant *GAA* gene transduction in the liver. He also asked the investigators to provide more detail about injection volume and injection depth calculations. Regarding potential anti-*GAA* immune responses that would render concurrent or subsequent Myozyme therapy ineffective, Dr. Bartlett asked the investigators to comment on their choice of the cytomegalovirus (CMV) promoter as opposed to a muscle-specific promoter, since it had been shown that restricting *GAA* expression to muscle tissue minimizes anti-*GAA* antibody response. He

asked whether it would be possible to distinguish residual participant *GAA* protein (from Myozyme therapy) from the *GAA* protein produced by the gene transfer vector and whether it would be possible to determine whether anti-*GAA* immune responses are directed against Myozyme protein or the *GAA* protein produced by gene transfer. If cellular immune responses or toxicities are observed, Dr. Bartlett asked whether serum and PBMCs would be collected for assessment.

Dr. Kodish asked the investigators to provide a more specific description of the background and training of the ombudsman who will oversee each research participant's interests and the process planned. He requested that language that suggests a primary goal of efficacy for this trial be altered, since the purpose of this study is to ascertain safety. Noting that an assent signature line is provided at the end of the informed consent document, Dr. Kodish suggested that a separate assent document or information sheet be provided for child-participants to accompany their signatures.

Dr. Yankaskas asked whether Myozyme administration induces *GAA* antibodies, and if so, how the investigators would distinguish them from those produced by the responses to the gene transfer CMV vector. He requested that the investigators discuss the sedation and anesthesia plans for vector administration to the diaphragm and whether the potential risks of these administrations are addressed in the protocol and in the informed consent document. Noting that the investigators will be analyzing the secondary outcomes of pulmonary function and phrenic nerve function, Dr. Yankaskas asked how the effects of muscle dysfunction related to disease progression or secondary infections would be considered.

Dr. Kishnani cited previous research in which switching the promoter to a muscle-specific version reduced the cytotoxic T-lymphocyte response and prolonged *GAA* expression in muscle, although high-titer antibodies were still formed; therefore, she asked the investigators to state their rationale for using a CMV promoter and noted that preclinical experiments in adult PD mice would be critical to evaluating the risk of cellular immune responses in humans with the disease. Enrollment criteria that raised questions for Dr. Kishnani included whether this protocol is appropriate for participants who are naïve to Myozyme but who are on a ventilator, whether individuals with high antibody titers to Myozyme would be included or excluded, the need for a clearer definition of "ventilator dependence," and why elevated transaminases is an exclusion criterion when transaminases are elevated in PD. Because children with PD, especially those with underlying cardiomyopathy, are at significant anesthesia and sedation risk, Dr. Kishnani asked the investigators to specify their sedation and anesthesia plans for vector administration to the diaphragm. In addition, she asked how antibodies to Myozyme administration would be distinguished from the responses to the CMV vector and what would be the timing of Myozyme infusion.

C. RAC Discussion

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

Dr. Yankaskas asked about the extent of diaphragmatic atrophy in the research participants and whether the surgeon would be able to assess the exact thickness of the diaphragm during the procedure.

Dr. Ertl asked whether the investigators would preserve participant blood samples. Doing so would permit future analysis, if, for example, 2 years after gene transfer some unexpected change occurs.

Dr. Wei asked about the possibility of using matched controls to analyze efficacy.

D. Investigator Response

1. Written Responses to RAC Reviews

Preclinical biodistribution studies have been conducted with AAV1 in three models using two control vectors and the test agent proposed for this clinical trial. The cumulative toxicology and biodistribution data, which have supported two other INDs, will be cross-referenced in the IND for this experimental agent. Species studied included mouse, rabbit, and rhesus macaque monkey; direct IM injection into the diaphragm has been done in the rabbit.

The investigators have not observed significant gene expression in the liver from AAV1 vectors delivered systemically. If transduction were to occur, there is no sustained gene expression from the CMV promoter in the liver.

All participants on Myozyme therapy have a significant humoral response to recombinant human *GAA*. The antibody response was associated with infusion associated reactions but did not prevent Myozyme administration in any of the trial subjects. Continuous intracellular production of vector-derived GAA is expected to have less of an impact on anti-GAA response. The investigators have not observed T-cell-mediated anti-*GAA* activity in humans or in mice receiving recombinant *GAA*. Cell autonomous expression of *GAA* will not expose the therapeutic protein to the circulation or to the extracellular space.

It will not be possible to distinguish residual patient GAA protein, from the GAA protein given therapeutically (Myozyme), and from the GAA protein produced by the gene transfer vector. The subjects eligible for the study are compound heterozygotes which express little or no endogenous GAA. Myozyme is delivered as a 110kDa precursor protein present in the circulation and processed in the cell to an active smaller form. The vector derived protein is also processed to the active form. The core protein from each source are all antigenically identical.

Antibody titers and peripheral blood lymphocytes will be monitored for response to human GAA for the duration of the study. The subjects will continue to receive Myozyme and it will not be possible to distinguish responses to the two proteins. The relative quantity of Myozyme produced within the cell and targeted to the lysosome is minimal compared to the high dose delivered intravenously.

The participants will receive general anesthesia for the proposed procedure using the method most acceptable to the supervising pediatric cardiac anesthesiologist. Since all the participants will be using invasive assisted ventilation as per the inclusion criteria, there is reduced risk associated with obtaining a secured airway. The risks are detailed in the informed consent document, and additional consultation with the anesthesiologist will occur preoperatively.

The contribution of phrenic nerve function to diaphragm function will be evaluated as a unit in the respiratory function tests to be conducted as secondary outcome measures. Direct measurement of phrenic nerve function is difficult to perform reliably without additional invasive procedures.

Because the participants in this trial will have reached a level of diaphragm and phrenic nerve dysfunction that has led to the need for continuous assisted ventilation, additional disease progression will not be possible to detect clinically. Therefore, change in secondary outcomes would be observed only if the gene transfer led to restoration of independent respiratory function. These changes would be subtle and would require additional respiratory strength training and rehabilitation.

2. Responses to RAC Discussion Questions

Assessing the amount of diaphragm atrophy at the time of surgery would be challenging, but the surgeon could make that assessment by direct inspection initially and then could assess the participant's suitability for the experimental procedure.

Dr. Byrne explained that it is difficult to define the exact significant cutoff amount of antibody levels for this trial. Some PD patients have high-titer antibodies with a favorable clinical response, and some patients have lower-titer antibodies with a worse clinical response; therefore, antibody levels will not be the sole criterion for participation in this trial. Potential participants who have severe manifestations of the disease and little chance to experience any secondary benefits of the gene transfer would not be included in this

study. The investigators would welcome additional analysis of the retrospective review of the immunologic data from the ERT studies to determine whether a relevant cutoff value exists that would provide added safety.

Regarding the definition of ventilator dependence, Dr. Bryne responded that the investigators define ventilator dependence as anyone who is invasively ventilated and who uses nighttime ventilation for more than 8 hours, even though some patients breathe independently when they are upright and awake.

Dr. Byrne agreed that animal studies giving the dose relevant to the clinical study will be conducted via IM delivery to assess the immune response. These studies will be completed and analyzed before commencing the clinical trial.

Dr. Byrne explained that no patients with this category of severe deficiency are usually alive after 12 months of age without therapy, and since the age inclusion criteria is 4 years, those potential participants must have been receiving some form of therapy that mitigates the fatal cardiac disease seen in this condition. He agreed to make explicit in the inclusion criteria that only individuals who have been on ERT for some length of time can participate in this trial.

One strategy for participants who are not sighted that is being used in the consent process of another of the investigators' studies is to provide an audio consent. This method may be more acceptable for some of the children in this proposed study who are not in school or may not be functioning at age level, so they can hear about the procedure and obtain more information.

With data from more than 600 PD patients entered in a long-term registry, Dr. Byrne agreed that comparison of registry data with the research participants' data might be useful, independent of the treatment modality the registry patients undergo.

E. Public Comment

George Fox offered written public comments. His son suffers from PD and is currently on an approved ERT as well as mechanical ventilation. Mr. Fox asked that the RAC assist Dr. Byrne in bringing this proposed approach to the clinic. Although his son's disease has slowed, his family is anxious for a new drug to emerge from the scientific arena.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

AAV vectors are known to elicit T-cell immune responses. In addition, a significant number of patients on ERT with systemic GAA develop antibodies to GAA. The transgene product is indistinguishable from the enzyme replacement product. Therefore, there is the potential that gene transfer could lead to immune responses to the vector and/or the transgene product, and GAA may decrease the efficacy of both gene transfer and ERT. To determine T-cell and antibody responses to the vector and the transgene product, additional preclinical studies should be conducted in rabbits using the same vector and route of administration proposed for this clinical trial.

Immune responses differ among neonates, children, and adults. Preclinical studies have been conducted only in neonatal mice. Therefore, additional studies of immune responses should be conducted in adult, immunocompetent GAA-knockout mice using IM vector delivery. These studies should provide more accurate predictive information for the proposed clinical study.

Clinical/Trial Design Issue

The immunological data collected in the trials studying ERT for PD should be reviewed to determine how GAA antibody titers affected clinical outcome. These results should be considered in determining whether an inclusion criterion based on GAA antibody titer should be added to this protocol.

Ethical/Legal/Social Issue

An assent document should be developed for minor children along with an information sheet or audio-recorded summary of the protocol to assist children who will be asked to assent. Guidance on analogous issues is available in the following article: Joffe S., *et al*., Involving Children With Cancer in Decision-Making About Research Participation, *J Pediatrics*, 149:6, 2006.

G. Committee Motion 5

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Dr. Strome moved and Dr. Ertl seconded the motion that the RAC approve these summarized recommendations. The vote was 18 in favor, 0 opposed, 0 abstentions, and 0 recusals.

X. FDA Regulatory Update: Foreign Trials for Investigational New Drugs (INDs)

Presenter: Donna Przepiorka, M.D., Ph.D., FDA

Dr. Przepiorka discussed changes to the FDA's "Guidance for Industry: Acceptance of Foreign Clinical Studies" regulations and data from foreign clinical trial sites for INDs. Foreign site clinical trial data enter the U.S. drug development process in three ways: (1) A foreign site participates in a multinational trial under a U.S. IND application; (2) data from an early-phase study performed at a foreign site are used to support late-phase studies under a new U.S. IND application; or (3) complete drug development is performed at a foreign site, and the data are submitted to support a U.S. license.

The number of foreign clinical investigators who conducted drug research under INDs increased from 41 in 1980 to 271 in 1990 and to 4,458 in 1999. From 1995 to 1999 approximately 35 percent of trials conducted under a U.S. IND application included foreign sites, and approximately 15 percent of trials submitted in new U.S. licensing applications were not conducted under a U.S. IND application.

A multicenter trial that involves a foreign site and is being conducted under a U.S. IND must follow the same regulations that U.S. investigators follow. Sponsors that have conducted all their work outside the United States and are applying for licensing will have to comply with 21 CFR 314.106, which includes a requirement to review the science and determine whether the population studied in the foreign country would be applicable to the U.S. population. Sponsors submitting data from clinical trials performed at a foreign site not under a U.S. IND application must comply with 21 CFR 312.120, which regulates conditions under which the FDA will accept data and includes a list of the supporting information to be submitted, the conditions under which a sponsor or applicant may ask the FDA to waive applicable requirements, and the need for record retention.

Effective August 27, 2008, and published in the *Federal Register*, a new rule regarding foreign trial data begins by stating that the FDA will accept data from a clinical trial conducted solely at a foreign site if the study was conducted in accordance with Good Clinical Practice (GCP). The rule defines GCP as the standard for the design, conduct, performance, monitoring, auditing, recording, and reporting of clinical trials in a way that provides assurance that the data and the results are credible and that the rights, safety, and well-being of trial participants are protected. These protections include review and approval by an independent ethics committee and documenting that freely given informed consent was obtained. The FDA has removed from the rule the text of the World Medical Association's Declaration of Helsinki;

however, the principles of the Declaration of Helsinki are preserved, and some of the specifics about conducting clinical trials have been expanded.

The FDA will accept data if it is possible to validate those data through an onsite inspection, so the rule provides for FDA inspection of clinical trials that were not conducted under a U.S. IND. The sponsor also is required to submit information to prove that the trial was performed under GCP, including descriptions of what was done, how it was done, what equipment was used, and who oversaw the trial.

The sponsor or the applicant may ask the FDA to waive some of the GCP requirements and the FDA may grant a waiver if it is in the interest of the public health, but a waiver is not likely except for minor technical issues. The new rule also includes a requirement for record retention that is more parallel to requirements for U.S. investigators.

XI. FDA Regulatory Update: FDA Guidance on Current Good Manufacturing Practice for Phase I Trials

Presenter: Daniel M. Takefman, Ph.D., FDA

Dr. Takefman discussed the Final Rule and Guidance for Current Good Manufacturing Practice (cGMP) for Phase I clinical trials. cGMP is a set of current, scientifically sound methods, practices, or principles that are implemented and documented during product development and production to ensure the consistent manufacture of safe, pure, and potent products. Drugs and biologics (including INDs) are required to be manufactured in accordance with cGMP.

The FDA published a Final Rule in the *Federal Register* to amend cGMP regulations for human drugs, including biological products, to exempt most investigational Phase I drugs from having to comply with the cGMP regulation. In addition to the Final Rule, the FDA published the companion guidance "cGMP for Phase I Investigational Drugs" to provide guidance for recommendations on approaches to statutory compliance for the manufacture of Phase I material. This guidance for Phase I INDs recognizes that some controls and the extent of controls differ between investigational and commercial manufacturing and among phases of clinical studies and articulates the expectation of greater control over the process through the various IND phases.

This new rule and its companion guidance are codifying what has been practice at the FDA. As clinical development proceeds, researchers are continually characterizing the product and process, leading eventually to full cGMP and full product characterization. Because it is difficult in the beginning to understand completely a complex biologic such as a gene transfer product and to have fully validated assays and a validated process, the FDA has never required cGMP to be followed completely in early-phase trials. Products made for early-phase trials are usually referred to as "clinical grade products."

Key points of the cGMP guidance are that effective quality control standards for Phase I include well-defined written procedures, adequately controlled equipment, and accurate and consistent recording of all manufacturing and testing data. It is expected that industry will implement cGMP consistent with principles of good scientific methodology, product development, and quality; avoid cross contamination; and prevent microbial contamination.

Phase II and Phase III manufacturing will continue to be subject to cGMP requirements. The FDA is considering issuing additional guidance and/or regulations to clarify FDA expectations with regard to fulfilling the cGMP requirements when producing investigational drugs for Phase II and Phase III clinical trials, but the timetable for issuing that additional guidance has not been set.

The biggest challenge with gene transfer products and cell therapy products is that is they are currently made primarily in academic facilities. Approximately 80 percent of the gene transfer products for use in clinical trials are being made in academic core facilities. To set up a significant jump in standards between Phase I and Phase II trials conducted at academic facilities may be more challenging compared with increasing requirements for other products that derive from manufacturing sources.

XII. Discussion of Human Gene Transfer Protocol #0807-923: Compassionate Trial of Nanocomplex-Mediated GNE Gene Replacement in Hereditary Inclusion Body Myopathy-2

Principal Investigator:	John J. Nemunaitis, M.D., Mary Crowley Cancer Research Centers
Sponsor:	Gradalis, Inc.
RAC Reviewers:	Dr. Federoff and Ms. Shapiro

Dr. Strome recused himself from consideration and discussion of this protocol due to a conflict of interest.

A. Protocol Summary

Hereditary inclusion body myopathy-2 (HIBM2) is a disease that causes severe skeletal muscle wasting and leads to almost complete disability as early as 35 to 45 years of age. No proven treatments exist for HIBM2.

Development of this disease is related to familial passage of a mutation of the *GNE* gene, which encodes the bifunctional enzyme UDP-GIcNAc2-Epimerase/ManNAc kinase (GNE/MNK). GNE/MNK is the rate-limiting bifunctional enzyme that catalyzes the first two steps of sialic acid biosynthesis. Decreased sialic acid production consequently leads to decreased sialylation of a variety of glycoproteins, including the critical muscle protein alpha-dystroglycan, which severely cripples muscle function and leads to the onset of this syndrome.

The investigators hypothesize that adding the normal *GNE* gene to replace the abnormal gene might restore minimal sialic acid production, enabling improvement in muscle function and/or delay in the rate of muscle deterioration. They have constructed a *GNE* gene/CMV promoter expression vector and have demonstrated enhanced *GNE* gene activity following delivery to *GNE*-deficient Lec3 cells, thus revealing that replacement with wild-type *GNE* cDNA restores GNE/MNK enzyme function.

The investigators propose to place the *GNE* expression vector in a liposome and to administer the resulting *GNE* lipoplex intramuscularly to test the safety and efficacy (measured as enhanced or stabilized muscle function) of *GNE* gene replacement in HIBM2.

B. Written Reviews by RAC Members

Six RAC members voted for in-depth review and public discussion of the protocol. Key issues included insufficient preclinical research, questions about the intervention's efficacy, the unlikelihood that generalizable knowledge would result from this intervention in one research participant, and ethical issues related to the investigators' involvement in the company that produces the vector being used in this study.

Requesting compassionate use, the PI had already received FDA approval and OBA allowed the investigators to begin dosing one research participant in August 2008.

Two RAC members provided written reviews of this proposed trial.

Dr. Federoff asked the investigators for evidence to support the supposition that restoration or stabilization of muscle function is possible in individuals with a progressive myopathy disease status as advanced as that of the intended participant. He inquired whether reestablishing the capacity to produce sialylated proteins could trigger immunological reactions due to new glycoepitopes, about the duration of expression beyond 2 weeks of the IM-delivered *GNE* lipoplexes, and whether injection of *GNE* lipoplexes would elicit more inflammation and possibly disease progression in the setting of profound muscle atrophy and necrosis. Dr. Federoff requested a rationale for the dose of *GNE* lipoplex selected below the no-observed-adverse-effect level and an explanation for the lack of an apparent dose relation between *GNE* injected and *GNE* expressed in mouse muscle.

Ms. Shapiro noted multiple conflicts of interest that pose serious concerns, including that the PI and the co-PI own majority stock in the sponsor and take part in managing the sponsor; the president of the site is also the president of the sponsor; and the site's vice president of research operations is the spouse of the PI (and also owns majority stock in the sponsor). Although the site's institutional review board (IRB) has determined that these potential conflicts do not pose additional risks to the participant and that it will oversee this study, she asked whether a review by a conflict of interest committee had occurred and requested a description of the result of that review. Ms. Shapiro also noted multiple safety concerns raised by the paucity of related preclinical research and the fact that this study is a single-participant protocol that cannot generate clinically relevant and reproducible data. Acknowledging that there exists no adequate animal model of the human disease, she requested additional information from the PI and from other members of the RAC as to the sufficiency of the preclinical data. Regarding the informed consent document, Ms. Shapiro stated that the discussion of the significant conflict of interest issues is vague, the discussion of risks and side effects is unclear, and the statement that the participant will be responsible for the costs of treatment for research-related injury raises ethical issues.

C. RAC Discussion

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

Dr. Ertl asked about the PI's plans for additional research after the experimental treatment time is completed.

Dr. Ertl requested additional information about the ethics of using a resesarch participant for the purpose of gaining data prior to proposing a full Phase I trial.

Given what the RAC has learned about HIBM2 and the disease community, Ms. Shapiro noted that the objective of clinical research ethics is not to eliminate conflicts of interest or to halt a trial but rather to manage those conflicts appropriately and to communicate clearly and fully how that management has been accomplished.

D. Investigator Response

1. Written Responses to RAC Reviews

In the intravenous immunoglobulin (IVIG) study involving advanced HIBM2 research participants treated with IVIG to provide a temporary source of sialic acid, modest benefit was demonstrated in muscle strength. The investigators acknowledged that individuals less severely affected with HIBM2 would likely provide greater opportunities for determination of efficacy.

No dominant negative missense or nonsense mutations have been reported. Since heterozygous individuals (ex. parents and siblings) do not show any evidence of muscle weakness, nature has provided some proof that there is no dominant negative effect.

The investigators explained the two reasons they believe that even relatively low levels of wild-type *GNE* will effectively restore normal sialic acid and sialylation: (1) Homozygous patients show only muscle disease, and *GNE* is expressed at relatively low levels in muscle; and (2) *GNE* has a negative inhibitory domain, so that a small amount of *GNE* is sufficient to produce a significant amount of sialic acid in a low sialic acid environment. The low levels of *GNE* in muscle fall below functional tissue demands, which may explain why it takes so long for the muscle pathology to develop.

Regarding the possibility of immune reaction to sialylated proteins, HIBM patients are reported to have normal serum sialic acid levels but muscle sialic acid levels 60-75% of both normal control and tissue culture levels. There is no evidence of an immune response to sialated moieties in the etiology of the disease. The mechanism for disease progression is unknown, so it may be that sialated epitopes gradually decline and newly sialated epitopes would not be considered foreign.

To determine the duration of expression beyond 2 weeks of the IM-delivered *GNE* lipoplexes, the investigators plan additional preclinical testing. In addition, Participant 1 will undergo day 3 and day 30 evaluations to determine *GNE* transgene expression, *GNE* protein level, and sialic acid activity.

Although it is possible that injection of *GNE* lipoplexes in the setting of profound muscle atrophy and necrosis could result in increased inflammation and disease progression, the investigators did not detect any such inflammation in treated normal mice. In addition, no inflammation was evident in the day 3 injection site biceps biopsy of Participant 1.

Regarding the dose of *GNE* lipoplex, the investigators explained that the IM dose in mice was 40 ug per muscle, and the IM dose in Participant 1 was 200 ug per muscle, for a total of 400 ug. However, the human muscles that each received the 200-ug dose are more than 20 times greater in length and corresponding volume compared with the murine muscle injected in the *in vivo* model, and the 200-ug human dose is spread over four injection sites at 2-cm intervals. The IV no-observable-adverse-effect level (NOAEL) dose in the mouse is 40 ug, with the human equivalent being approximately 160 mg in an 80 kg human. Thus, the total dose Participant 1 received was 400 ug, which is 400 times lower than the systemic NOAEL.

Regarding conflict of interest, the investigators explained that they were not majority stockholders of the sponsor, but agree with the perceived potential for conflict of interest and instated Dr. Joseph Kuhn as the PI of the single patient IND. Dr. Kuhn, a surgeon with no ties to Gradalis, Inc. or Mary Crowley Cancer Research Centers, administered the GNE-lipoplex. Furthermore, the subject's long term neurologist has maintained monitoring of the subject. His report is consistent with our muscle function tests. He, too, has no ties to Gradalis or Mary Crowley. Study sites outside of Mary Crowley will be used for subsequent phase trials.

2. Responses to RAC Discussion Questions

Dr. Nemunaitis described the investigators' plans for proceeding after the 2-week period of benefit experienced by Participant 1 in this compassionate trial. The investigators intend to complete the safety database in mice to begin discussing an IV infusion trial. In the specific case of Participant 1, the investigators plan to administer intravenously a lower dose than was given as an IM dose; eventually, they will raise that dose in Participant 1. The IV administration and the increased dose will be designed into an amendment to this protocol after completion of additional animal data. They hope that the database generated from Participant 1's additional IV dosing, as well as subsequent animal studies, will provide sufficient data for a Phase I trial involving IV dosing and a traditional three-participant dose-escalation trial at three sites.

In answer to the RAC's concerns about conflict of interest in this single subject exemption trial, Dr. Nemunaitis explained that his oncology program has a great deal of genomics experience. Participant 1 is a friend, so the technology of that program was used to try to help this individual. He intends that all subsequent participants will be treated at neuromuscular centers, several of which have already been identified, and potential participants will be assessed by third parties from outside the neuromuscular centers. There is no opportunity to generate business revenues from the treatment of this disease.

E. Public Comment

Dr. Borror noted that the informed consent document contained some incorrect numbers in the section on description of risks as well as some overly complex language.

Julie Osborne, via teleconference, offered her comments to the RAC. She is "Participant 1," who has already been dosed in this trial. She reiterated her extensive experience in the research field of cancer and muscular dystrophy as a working research nurse and now as a member of two IRBs. Ms. Osborne's goal for participating in these studies is to increase research for HIBM2, and she stated her full awareness that this compassionate trial might not generate anything that would benefit her, which was

stated in the informed consent document. Ms. Osborne's goal is to further the research and to help other patients not to become as affected as she is.

Manny Yashari, an obstetrician/gynecologist in Los Angeles, California, spoke on behalf of his daughter Jennifer, who is a psychiatrist and who was diagnosed with HIBM2 approximately 4 years ago. She has gotten progressively worse in the past 2 years; causing difficulties in caring for her young child, and she is no longer able to practice psychiatry. HIBM2 is more prevalent than the statistics that show only 265 people affected in the world. Dr. Yashari cited several of his relatives who are affected by this disease, quite a few patients in Los Angeles, and Tel Aviv and New York, and 150 families in Japan who have the mutation of the HIBM2 gene. He read parts of his daughter's remarks, which were written 1 year ago:

> "Living with a progressive neuromuscular disease means constantly having to cope with and adjust to new losses of function of various parts of my body. Just when I was finally able to accept that I could only walk slowly because of the weakness in my legs, I started to lose the strength in the fingers of my left hand. Just when I thought my symptoms had plateaued for a while, I realized that I had atrophy or muscle wasting in my forearms and upper legs. With a disease of this nature there's no such thing as a remission. No period of time when you are symptom free and get to do all the things that you used to love and there's no escape. Not mentally or physically. From the moment I wake up in the morning and monitor whether anything is weakened, through every step I take throughout the day, to trying to lie in a comfortable position in bed at night it's there. Every time I have trouble snapping my son's pajamas or lifting him off the floor or carrying him asleep from the car to our home, I wonder for how much longer are you able to do things like that. My right arm is only minimally weak now, but how much longer until I have trouble turning the key in the ignition or pulling my foot up off the gas pedal? …

Dr. Yashari emphasized the need for a cure. In the world's Jewish community, 1 out of 15 people carries this disease, and 25 percent of carrier offspring are infected with HIBM2. Statistics regarding the prevalence of the disease may not be accurate because unfortunately, some communities do not want to acknowledge the presence of this disease in their culture.

Gwen Van Duyn offered remarks related to her two sons Garret and Wym, both of whom have HIBM2 and were present; her husband, John Van Duyn, was also present. In HIBM2, time is of the essence. The average age of onset is about 26 years of age; both Garret and Wym had onset at about that time. The average person is wheelchair bound within 10 to 12 years. The research in the United States is negligible with the exception of what Dr. Daniel Darvish and his brother, who is also affected, have been able to do in southern California and the research of Dr. Nemunaitis. Ms. Van Duyn noted a research focus in Israel because of the Persian-Jewish ethnic component of this disorder as well as a big research push in Japan, but little research on HIBM2 is being conducted in the United States because it is an orphan disease. Although Ms. Osborne may not expect to benefit personally, Ms. Van Duyn stated that the people with PD who still have some ambulatory ability could benefit tremendously.

John Van Duyn added to his wife's testimony that, at some point in the future, additional gene transfer research in HIBM2 may benefit the many individuals suffering from diseases that involve some of the same physiologic pathways.

Daniel Darvish, M.D., an HIBM2 patient for the past 15 years, started a nonprofit organization to fund research. He noted several key issues with regard to this "ultra-orphan disease." Worldwide prevalence of HIBM2 is approximately 1,000 known patients; therefore, the conflict of interest rules and the decisions made by the RAC should be different from those considered for more common disorders. The potential for profit is almost nonexistent worldwide when compared with the cost of research and development, which changes the potential ethical issues. Dr. Darvish stated that the amount of preclinical data needed to determine efficacy and toxicity must be considered in the context of what the patients are going through, the urgency to develop a therapy, and the kind and level of risks the patient population is willing to take.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

Patients with HIBM have extremely low levels of sialylated glycoproteins. Additional preclinical models should be used to determine whether the increased production of sialylated proteins could trigger immunological reactions due to new glycoepitopes.

In the preclinical mouse studies, the expected dose relationship between the amount of the *GNE* vector injected and *GNE* protein expression was not seen. Additional preclinical studies should elucidate the dose relationship and why increasing the amount of vector does not appear to affect expression.

Clinical/Trial Design Issues

In any subsequent clinical trials, studies should be undertaken to determine whether different mutations in the *GNE* open reading frame would alter the anticipated clinical effects of expressing a fully wild-type and functional protein. However, such studies would necessitate muscle biopsies.

Although the investigators presented data suggesting that Participant 1 may have experienced some functional improvement in the injected muscles, the changes may not have been due solely or at all to *GNE* expression. If Participant 1 is to be dosed again, additional analysis should be carried out to determine what role the *GNE* gene played in the improvement. Using a control injection might be necessary.

Ethical/Legal/Social Issues

There are a number of conflicts of interests, perceived and real. Dr. Nemunaitis is a shareholder in the company, Gradalis, Inc., that developed the vector, and he is involved in its management. The president of the Mary Crowley Cancer Research Centers is also the president of Gradalis, and the Mary Crowley Cancer Research Centers' vice president of research operations, who oversees compliance with Federal and State laws, is the spouse of Dr. Nemunaitis. The appointment of a new PI does not fully resolve the issues, because Dr. Nemunaitis continues to be involved in participant recruitment and data analysis. In addition, the statement in the informed consent document that "the IRB has determined that these potential conflicts do not pose additional risks to the subject" is not a sufficiently detailed explanation given the complexity of the relationships. In the future, these conflicts should be minimized if additional participants are enrolled. To the extent that these conflicts cannot be eliminated, a more detailed explanation of their potential impact should be included in the informed consent document.

A Phase I trial of this vector is planned in the same patient population. If the current informed consent document is adapted for that trial, certain technical terms should be simplified.

G. Committee Motion 6

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Ms. Shapiro moved and Dr. Kirchhoff seconded the motion that the RAC approve these summarized recommendations. The vote was 14 in favor, 0 opposed, 0 abstentions, and 1 recusal.

XIII. Discussion of Single-Participant Human Gene Transfer Trials ("Compassionate Use") and the Role of the RAC

Presenter: Dr. Corrigan-Curay
Moderator: Dr. Federoff

A. Presentation

Dr. Corrigan-Curay provided a summary of the OBA's review process for single-participant protocols. Single-use protocols are often exceptions to the protocol design the RAC usually reviews, involve judgments about the suitability of gene transfer for an individual patient based on her or his unique clinical circumstances, and are usually time sensitive. Such protocols may be determined to be an amendment to an existing protocol or a new protocol depending on whether the same vector has been used in a research protocol the RAC had the opportunity to review, and the parent protocol, modified as needed, is used for the single subject. For amendments, OBA can consult with the clinicians on the GTSAB and provide feedback in a timely manner to the PI and IBC Five single-participant protocols have been sent to the RAC for full review as new protocols since 2003. Protocol 923 is the first to be reviewed in public since 1993.

Questions for consideration include whether public discussion of single-participant protocols serves the RAC's primary mission to promote safe and ethical research and to inform the scientific community and the public, whether the RAC is an appropriate body to make these decisions, and whether the RAC's process accommodates these reviews. As an advisory body to the NIH, the RAC does not approve or disapprove protocols. The RAC's primary focus is on research, including protocol design and safety, and the RAC process has mandated timeframes. A central question is whether single-participant protocols should be considered "research" or "treatment."

The OBA's proposals are to post frequently asked questions on single-participant protocols to the OBA Web site, clarifying that submission of information on such protocols should be done in a timely manner and that the OBA will determine whether to treat submissions as new protocols or as amendments. In relation to the RAC, the OBA proposes that the majority of single-participant protocols continue to be treated as amendments, but certain single-participant protocols will become new OBA registered protocols and will be reviewed by the RAC. If a protocol is treated as an amendment, the OBA will consult with the RAC's GTSAB as needed and will provide timely feedback to the investigators. In the case of a new protocol undergoing initial RAC review, comments received from individual RAC members will be transmitted by the OBA to the PI, the institutional biosafety committee (IBC), the IRB, and the FDA. Full RAC review and discussion of such protocols at a public meeting will be the exception.

B. RAC Discussion

RAC members discussed the issues and the OBA's proposals, including whether the RAC's process accommodates these reviews, whether RAC members view the RAC as qualified as an advisory body to take on the role of reviewing these kinds of protocols, the definition of research, responsibility for public health safety vs. participant safety, distinguishing between treatment and an attempt to develop research, time sensitivity issues, and creation of an *ad hoc* committee of RAC.

C. Public Comment

Dr. Takefman explained that the FDA has been receiving emergency requests for products that have never been tried clinically. The bottom line is always the same: The requester must submit a full IND, with full supporting pharmacology and toxicology information. If a full IND does not exist, then the FDA will not approve the product for any use in humans. Having the full toxicology study to submit to the FDA for review is the major regulatory hurdle in these situations.

D. Committee Motion 7

Dr. Federoff asked for a vote on the recommendation that the OBA consider a new method of dealing with single-participant protocols that would possibly include creation of an *ad hoc* or standing committee of the RAC, including at least one member of the RAC's GTSAB. Without an official move or second that the RAC approve this recommendation, the vote was 12 in favor, 0 opposed, 0 abstentions, and 0 recusals.

XIV. Followup on *NIH Guidelines for Research Involving Recombinant DNA Molecules*: Noncontemporary Influenza and Highly Pathogenic Avian Influenza

Presenter: Dr. Kanabrocki

A. Presentation

Research into viral virulence mechanisms and the development of vaccines and antiviral drugs are public health priorities. Although this research is of critical importance, it is equally important that the research be performed under appropriate biocontainment conditions to protect the health of laboratory researchers and the public. The RAC's Biosafety Working Group (BWG) was asked to provide biosafety and containment guidance for recombinant research with noncontemporary human influenza virus H2N2, fully reconstructed 1918 H1N1 influenza virus, and highly pathogenic avian influenza virus H5N1. The BWG considered current guidance provided by the Centers for Disease Control and Prevention (CDC)/NIH *Biosafety in Microbiological and Biomedical Laboratories* manual (BMBL) and the U.S. Department of Agriculture (USDA) Animal and Health Inspection Service, consulted influenza experts, and reviewed additional scientific data.

Dr. Kanabrocki summarized the BWG recommendations for revisions to the *NIH Guidelines*. Non-contemporary human influenza virus H2N2, fully reconstructed 1918 H1N1 influenza virus, and highly pathogenic avian influenza virus H5N1 would be classified as RG 3 agents. Biosafety level 3 (BL-3) containment with the enhancements described in BMBL (e.g., additional respiratory protection and clothing change protocols, etc.) was recommended for work with each virus. In general, recombinant work with these viruses will be at BL3 enhanced except in certain limited cases (e.g., work with cold-adapted, live attenuated vaccine strains). For research with 1918 H1N1, recommendations were proposed similar to those of the CDC Medical Surveillance Program including the use of pre-exposure antiviral prophylaxis. Containment for work covered under the CDC or the USDA Select Agent Rule will continue to be set by the CDC or the USDA.

Given the current limited ability to predict the phenotype of recombinant influenza viruses containing some segments, or genes from 1918 H1N1 or H5N1 viruses and the lack of consensus on the data necessary to conduct an adequate risk assessment, all recombinant research involving such viruses should be conducted using the containment levels and practices recommended for the higher RG source virus (BL3+). If data becomes available to suggest that any specific line of experimentation could be safely conducted at lower containment, investigators are encouraged to submit relevant information on the proposed experiment to NIH/OBA. The decision to lower containment will be determined by NIH/OBA in consultation with the RAC and *ad hoc* experts. This process ideally would create a risk assessment framework that might allow these decisions to return to local IBCs in the future.

B. RAC Discussion

RAC members and the discussants talked about the issues, including concern about the safety of oseltamivir as prophylaxis for laboratory workers, distinguishing between highly pathogenic and nonpathogenic avian strains for H5N1, and the relative risks in the community of contracting H1 vs. H2 viruses. Dr. Ertl and Dr. Roizman requested greater specificity of the strains of H2N2 or H5N1 as those that have caused human disease for consideration as RG 3 agents.

C. Public Comment

Brian R. Murphy, Kanta Subbarao, and Jeffery Taubenberger, NIAID, NIH and James Schmitt, OD, NIH expressed concerns about requiring long-term use of antiviral drugs. Use has only been approved for up to six weeks by the FDA. They did not consider the risk to lab workers to be balanced by potential benefit to the public.

D. RAC Recommendations

Dr. Federoff summarized the RAC discussion by thanking the BWG for its work and noting that its work is not yet complete. Other facets that need consideration include the following:

The BWG should harmonize its recommendations with regard to appropriate treatment vs. prevention by inviting others to join the BWG to arrive at a consensus opinion.
There is no absolute threshold in terms of the number of genes identified as compelling a need for increased biological containment. If the threshold is too arbitrary, some research will be compromised.
The H2 strains should be defined more precisely.
A risk-benefit analysis should be used to determine whether prophylaxis is appropriate, regardless of the logistical issues involved.

After considering these issues, the BWG will return to the RAC with revised recommendations.

XV. Closing Remarks and Adjournment

Dr. Federoff thanked the RAC members and OBA staff and adjourned the meeting at 4:30 p.m. on September 10, 2008.

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

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

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

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

Date: _____

_____
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Attachment I
Recombinant DNA Advisory Committee Roster

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Attachment II
Public Attendees

Paul S. Aisen, University of California, San Diego
David Barba, University of California, San Diego *(via teleconference)*
Raymond T. Bartus, Ceregene, Inc.
Valerie Bonham, Office of the General Counsel (OGC), NIH
Dirk G. Brockstedt, Anza Therapeutics, Inc.
Gary Buchschacher, Jr., University of California, Los Angeles/Southern California Permanente Medical Group
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Andrea L. Cox, Johns Hopkins University
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George Fox, private citizen
William Gahl, National Human Genome Research Institute (NHGRI), NIH
Marty Giedlin, Sangamo BioSciences, Inc.
Robyn Goldman, Capital Consulting Corporation (CCC)
Hallie Heaney, University of Maryland
Ying Huang, FDA, DHHS
Laurent Humeau, VIRxSYS Corporation
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Jeffery Taubenberger, NIAID, NIH
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John Tonkiss, OD, NIH
Garret Van Duyn, private citizen/HIBM Research Group
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John Van Duyn, HIBM Research Group
Wym Van Duyn, HIBM Research Group
Jan Vleck, Institutional Biosafety Committee Services
Samuel C. Wadsworth, Genzyme Corporation
Gladice Wallraven, MCCRC
Gretchen Weaver, OGC, NIH
Fofie Witter, CCC
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Manny Yashari, private citizen

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
ABSL	animal biosafety level
AD	Alzheimer's disease
ADAC	Antiviral Drugs Advisory Committee (FDA)
AE	adverse event
Anza	Anza Therapeutics, Inc.
BSL	biosafety level
BWG	Biosafety Working Group (a subcommittee of the RAC)
CDC	Centers for Disease Control and Prevention (DHHS)
cDNA	complementary deoxyribonucleic acid
cfu	colony-forming unit
CGMP	Current Good Manufacturing Practice
CMV	cytomegalovirus
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
ERT	enzyme replacement therapy
FDA	Food and Drug Administration, DHHS
GCP	Food Clinical Practice
GNE/MNK	bifunctional enzyme UDP-GIcNAc2-Epimerase/ManNAc kinase
GTSAB	Gene Transfer Safety Assessment Board
HCC	hepatocellular carcinoma
HCV	hepatitis virus type C
HIBM2	hereditary inclusion body myopathy-2
IBC	institutional biosafety committee
IFN	interferon
IFN-□	IFN-alpha
IM	intramuscular
IND	investigational new drugs
IRB	institutional review board
IV	intravenous
IVIG	intravenous immunoglobulin
LAR	legally authorized representative
Lm	*Listeria monocytogenes*
MacCAT-CR	MacArthur Competence Assessment Tool for Clinical Research
MCCRC	Mary Crowley Cancer Research Centers
MD	muscular dystrophy
MSSM	Mount Sinai School of Medicine
MTD	maximal tolerable dose
NGF	nerve growth factor
NHGRI	National Human Genome Research Institute, NIH
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NK	natural killer
NOAEL	no-observable-adverse-effect level
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
OGC	Office of the General Counsel, NIH
PBMC	peripheral blood mononuclear cell
PD	Pompe disease
PET	positron emission tomography

PI	principal investigator
rAAV1-CMV-GAA	recombinant adeno-associated virus acid alpha-glycosidase
RAC	Recombinant DNA Advisory Committee
RG	Risk Group
RNA	ribonucleic acid
rVSV(MΔ51)-M3	recombinant vesicular stomatitis virus
SOC	standard of care
UCSD	University of California, San Diego
USDA	U.S. Department of Agriculture
VSV	vesicular stomatitis virus