RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 8-9, 2004

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

CONTENTS

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

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

June 8-9, 2004

The Recombinant DNA Advisory Committee (RAC) was convened for its 96th meeting at 8:30 a.m. on June 8, 2004, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Diane Wara (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:30 a.m. until 4:30 p.m. on June 8 and from 9:00 a.m. until 12:35 p.m. on June 9. The following individuals were present for all or part of the meeting.

Committee Members

W. Emmett Barkley, Howard Hughes Medical Institute
Martha C. Bohn, Northwestern University
James F. Childress, University of Virginia
Neal A. DeLuca, University of Pittsburgh
David L. DeMets, University of Wisconsin Medical School
Thomas D. Gelehrter, University of Michigan Medical School
Helen Heslop, Baylor College of Medicine
Larry G. Johnson, University of North Carolina, Chapel Hill
Terry Kwan, TK Associates
Maxine L. Linial, Fred Hutchinson Cancer Research Center
Bernard Lo, University of California, San Francisco
Nicholas Muzyczka, University of Florida
Glen R. Nemerow, The Scripps Research Institute
Madison Powers, Georgetown University
Robert D. Simari, Mayo Clinic and Foundation
Diane W. Wara, University of California, San Francisco

Office of Biotechnology Activities Director

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

RAC Executive Secretary

Stephen M. Rose, OD, NIH

***Ad Hoc* Reviewer/Speaker**

Stephen D. Miller, Ph.D., Northwestern University

Nonvoting/Agency Representatives

Kristina C. Borror, Office for Human Research Protections (OHRP)
Maritza McIntyre, U.S. Food and Drug Administration (FDA)

[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 Staff Members

Robert Baughman, National Institute of Neurological Disorders and Stroke
Maria Cristina Cassetti, National Institute of Allergy and Infectious Diseases (NIAID)
Susan Emmett, OD
Kelly Fennington, OD
Robert Jambou, OD
Emily Katz, OD
Mary Leinhos, OD
Laurie Lewallen, OD
Daniel Lipton, OD
Cheryl McDonald, OD
Maureen Montgomery, OD
Brian Murphy, NIAID
Marina O'Reilly, OD
Alexander Rakowsky, OD
Gene Rosenthal, OD
Thomas Shih, OD
Kanta Subbarao, NIAID
Frosso Voulgaropoulou, NIAID
Gisele White, OD

Others

There were 92 attendees at this two day RAC meeting. Attachment I contains a list of RAC members, an *ad hoc* reviewer/speaker, nonvoting/agency liaison representatives, and Office of Biotechnology Activities (OBA) staff members. Attachment II contains a list of public attendees.

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

Dr. Wara, RAC Chair, called the meeting to order at 8:30 a.m. on June 8, 2004. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* was published in the *Federal Register* on May 19, 2004 (69 FR 28935). Issues discussed by the RAC at this meeting included public review and discussion of five protocols, a data management report, update on the RAC Gene Transfer Clinical Trial Design Working Group, update on a gene transfer protocol first reviewed by the RAC in September 2001, and an introduction to the upcoming safety symposium on research with pathogenic viruses.

Dr. Rose reminded RAC members of the rules of conduct that apply to them as special Federal Government employees.

II. Minutes of the March 9-11, 2004, RAC Meeting/Drs. DeMets and Linial

Drs. DeMets and Linial thanked the NIH OBA staff for the complete and well-written minutes. A few spelling changes were suggested.

A. Committee Motion 1

It was moved by Dr. Linial and seconded by Dr. DeMets that the RAC approve the March 9-11, 2004, RAC meeting minutes. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Update on Protocol #0107-488: A Phase I, Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous CD4 T Cells Transduced with VRX496 in HIV-Positive Subjects

Presenter:	Boro Dropulic, Ph.D., VIRxSYS Corporation
Additional Presenter:	Tessio Rebello, Ph.D., VIRxSYS Corporation
Sponsor:	VIRxSYS Corporation

(In-depth review and public discussion of this protocol occurred at the September 2001 RAC meeting.)

Dr. Dropulic reviewed the protocol and the rationale behind it. Protocol #0107-488 is a phase I trial to evaluate a single dose of HIV-derived lentiviral vector carrying an antisense sequence targeted to HIV in the treatment of HIV infection. Participants' CD4 T cells are transduced *ex vivo* with the vector, expanded for 8-11 days, and then the modified cells are reintroduced into the participants. Each participant receives a single intravenous injection of one of four ascending doses (1×10^9, 3×10^9, 1×10^{10}, and 3×10^{10} cells/subject). The primary objective of the study is to determine the safety and tolerability of treatment with autologous CD4+ cells transduced ex vivo with VRX496 when administered to HIV infected participants. A secondary goal of the study is to determine whether autologous CD4 T cels transduced with VRX496 are effective in preventing productive HIV replication, thus permanently decreasing viral loads to levels at which AIDS disease progression will be postponed indefinitely. This Phase I clinical trial enrolls participants without available, potentially positive treatment options.

Dr. Dropulic explained the vector structure, procedures for producing vector that can be administered to participants, and the efficient transduction levels. The antisense RNA, almost a kilobase in length, offers many regions of homology that could bind and inhibit the wild-type HIV RNA. Two similar vectors are used—VRX496, which has been used in the clinic, and VRX494, which is an analogous vector that expresses green fluorescent protein used for genetic marking in preclinical studies. To measure the vector's ability to inhibit HIV replication, CD4 T cells were isolated from the blood of uninfected individuals and divided into two lots. Vector was added to one of the lots, both lots were challenged with strains of HIV. The amount of HIV P24 protein was assayed in the supernatants of the cells as a measure of HIV replication.

Representative data from a cohort of 20 participants was shown. Research participants were enrolled with a range of viral loads and CD4 T cell counts. Results showed that the vector expressing the HIV antisense sequences inhibited viral replication in participants with both high and low viral loads and high and low CD4 T-cell counts. Other results indicated that multiple copies of the vector are needed for efficacy and that the HIV virus becomes less fit for replication as it accumulates more mutations. The participants experienced no adverse events (AEs) related to the infused product. No evidence of emergence of replication competent lentivirus was detected (i.e., ELISAs to detect antivesicular stomatitis virus G protein (VSVG) antibodies were negative, and no VSVG nucleic acids were detected in the participants' cells or plasma). No change was seen in the participants' T-cell repertoire or anti-HIV immune response. The viral loads of the first three participants are lower than baseline before T cell infusion at the various analysis time points; however, the significance of this decrease has not been established given the small number of participants and the intrinsic variability of viral load data. The investigators noted that, after 270 days, transduced cells were still detectable in participants.

Dr. Dropulic provided a summary of the preclinical, nonhuman animal data, participant characteristics, visit schedule and monitoring. The first research participant was dosed in July 2003. To date, no AEs related to the infused product have been observed, and the CD4 counts for the first three participants have remained stable. The data and safety monitoring board (DSMB) has recommended dosing of participants 4 and 5 based on the safety profile of participants 1, 2, and 3.

Two Phase II clinical trials are planned to follow-up this trial. These open-label, multicenter, multiple-infusion, Phase II clinical trials will be conducted at two sites in South Africa and the United States. Participants in South Africa will be treatment naive, and U.S. participants will have failed one highly active antiretroviral therapy regimen. Participants will receive up to eight infusions (two cycles of four infusions each).

A. RAC Discussion

Questions from RAC members included the following:

- Dr. Linial asked for additional details about the assay used for assessing recombination of vector sequences. Dr. Dropulic responded that either the vector or the cell product is added to a sensitive T-cell line called CA166 and the exposed cells are passaged 10 to 12 times for about 6 weeks. A Taqman real-time polymerase chain reaction (PCR) assay then is used to detect either *gag* in the vector product or VSVG in the cell product, which would indicate viral recombination leading to replication. If either is detected, the product is not released.

- Dr. DeLuca asked whether cells that become infected with the vector survive and function as normal cells. Dr. Dropulic stated his belief that these cells function normally, but that the investigators are currently examining that question.

- Dr. Lo asked whether the South Africa participants have access to what would be considered standard antiretroviral regimens in the United States or northern Europe. Dr. Dropulic answered that he did not know since there is a lack of those drugs in South Africa; he said he would discuss this issue with his collaborators.

- Dr. DeLuca asked whether, in the transduced, HIV-infected T cells from the participants, the infection is aborted before or after integration. Dr. Dropulic explained that infection is aborted after integration. The investigators are in the process of determining whether the cells survive because the infected cells could be a reservoir of HIV genomes.

- Dr. DeMets asked for more information about the toxicity or tolerability measures that would influence the investigators' decision to move to the next clinical trial phase. Dr. Dropulic noted that those parameters were already in place for the Phase I clinical trial, and if any of those toxicity or tolerability measures were encountered, the clinical trial would not go forward.

- Ms. Kwan suggested that the participants in the South Africa site might be subjected to a less coercive choice to participate in the trial if they were offered equal opportunity to have the standard regimen and the experimental regimen, since the standard regimen is not generally available to the population in South Africa. Dr. Rebello explained that the South Africa Government will be offering antiretroviral drugs to HIV-infected persons with CD4 T-cell counts of 250 and below, whereas this clinical trial will enroll participants with CD4 T-cell counts of 350 and above; therefore, "treatment" is being offered through this clinical trial to individuals who would not otherwise have access to antiretroviral regimens in South Africa. He also noted that, at the request of the South Africa Government, the investigators have agreed to follow these participants yearly for 15 years.

B. Public Comment

No comments were received from the public.

IV. Discussion of Human Gene Transfer Protocol #0404-642: A Phase I Trial of Gene Transfer during Ventricular Assist Device Support with SERCA2a

Principal Investigator: Barry London, M.D., Ph.D., University of Pittsburgh Medical Center
Additional Presenters: Roger J. Hajjar, M.D., and Xiao Xiao, Ph.D., University of Pittsburgh

RAC Reviewers: Drs. L. Johnson, Lo, and Simari

Dr. DeLuca, Ms. Kwan, and Dr. Powers recused themselves from the discussion of this protocol.

A. Protocol Summary

Heart failure from heart attacks and other heart muscle diseases affects millions of people in the United States. Despite recent advances in treatment, the 5-year survival rate for severely affected individuals remains below 50 percent. Ventricular assist devices (VADs) (partial artificial hearts) are used in patients with end-stage heart failure as a bridge to heart transplant. Only a small fraction of patients on VADs recover sufficiently for the devices to be successfully removed, and insufficient numbers of donor hearts are available for transplant.

The sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) is a protein that pumps calcium into the storage compartment in heart cells. The protein is deficient in patients with heart failure. Restoring SERCA2a levels using gene transfer has been shown to improve heart function in nonhuman animal models of heart failure and the strength of contraction in heart cells isolated from humans with heart failure. The investigators propose a Phase I trial at two sites (University of Pittsburgh and Massachusetts General Hospital) to test the safety of expressing SERCA2a using gene transfer in heart failure patients who receive VADs in anticipation of a heart transplant. At the time the VAD is placed, eight research participants will receive SERCA2a gene transfer; eight others will not receive the experimental agent. The participants will be followed for evidence of complications related to the experimental gene transfer. The investigators will determine whether gene transfer with SERCA2a improves heart function compared to that of control individuals who didn't receive the experimental agent using echocardiograms and stress tests. At the time of heart transplant, the native heart will be removed, the amount of extra SERCA2a expression will be determined, and changes in the structure of the heart will be identified.

B. Written Reviews by RAC Members

Twelve RAC members recommended in-depth review and public discussion of the protocol. The vector and transgene have not been used previously in humans for congestive heart failure, and the preclinical studies of this vector appear somewhat limited. RAC reviewers Drs. L. Johnson, Lo, and Simari submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. L. Johnson noted that the design of this proposed study is actually more consistent with that of a Phase II or a hybrid Phase I/II rather than a typical Phase I study. Dr. L. Johnson questioned the rationale for the lack of a dose escalation component in the study design. He asked about the percentage of participants expected to survive and reach transplantation, which impacts on the investigators obtaining tissues for histology and gene expression studies. He was satisfied with the Investigator's response of an anticipated rate of 80%. He questioned the potential for lateral spread of the vector from injection sites that might confound the interpretation of results from adjacent non-injected myocytes. He asked for further explanation of the assessment of regional wall motion using Doppler ECHO and whether that could truly make a quantitative assessment. In the written response, the investigators explained the Doppler ECHO procedure and how the data will be analyzed and the statistical methods of data analysis. Dr. L. Johnson noted that the biodistribution studies with the actual vector to be used clinically were still pending and that data would be important to have prior to starting the clinical study. He noted that safety endpoints and stopping rules should be defined up-front to provide more guidance to the investigators and the Data and Safety Monitoring Board. Dr. L. Johnson also questioned the risk of perforation and how the depth of penetration is controlled with the intramyocardial injections. Dr. L. Johnson noted some overly optimistic language in the informed consent document as well as a discrepancy in the planned duration of record retention and patient follow-up. The investigators agreed to replace the term "gene therapy" in the consent form and remove references to treatment that suggest benefit.

Noting that a potential adverse effect of adeno-associated virus (AAV) is inflammation in the liver and kidneys, Dr. Lo wondered whether persons with abnormal liver function tests or elevated creatinine levels at baseline should be excluded from this trial. The investigators explained that participants with only mild liver dysfunction will not be excluded the protocol. Dr. Lo questioned whether RV dysfunction is a potential adverse event that needs to be added to the Informed consent document (ICD), and noted that because arrhythmias could arise, the ICD should mention that there is a possibility that the subject could be harmed. Like the other reviewers, he too noted that some of the language in the consent form was overly optimistic and terms more in keeping with the experimental nature of this protocol should be employed. The investigators agreed to amend the ICD to include a statement about the potential risk of arrhythmias and the experimental nature of the protocol.

Dr. Simari focused his review on three areas: the preclinical studies, the clinical proposal, and the informed consent document. With respect to preclinical data, Dr. Simari noted that insufficient preclinical data with the proposed vector were included to allow an assessment of the risks of this proposed study. He questioned if preclinical studies with left ventricular assist device (LVAD) implantation, immunosuppression, or with the proposed means of delivery had been performed. Regarding the clinical proposal, he questioned how the number of participants was determined; what the chances of weaning the LVAD were in this population and whether long-term delivery has been modeled; what the risks of infection are during device implantation; and how the dosing design would affect the interpretation of the safety data. Regarding the Informed Consent Document, Dr. Simari noted that any real or perceived conflicts of interest of the investigators should be disclosed, that it should be clear this is the first use of AAV6 in man, and that some of the language in the consent should be brought in line with the experimental nature of this investigation.

C. RAC Discussion

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

- Dr. L. Johnson asked whether systemic toxicity information would be learned from the lower dose.

- Dr. DeMets suggested involving a statistician in the design and analysis and also on the monitoring committee.

- Dr. Nemerow asked whether, in the pig model, the investigators had checked for AAV6 antibodies or the transgene or whether that is planned for the future canine studies.

- Dr. Simari noted that he would favor designing the preclinical studies as closely as possible to represent the clinical study, perhaps involving consideration of extending the studies to longer term or performing preclinical studies with immunosuppression. He also suggested reevaluating the number of subjects planned, especially with regard to the need for eight control subjects.

D. Investigator Response

Dr. London and colleagues responded with the following information:

- Neutralizing antibodies to AAV have been found in other models, and the investigators plan to look in the dog model for antibodies to both SERCA and AAV. In the pig model, no neutralizing antibodies have been found, although SERCA2a has been found in the serum.

- Regarding toxicity information learned from the lower dose, an algorithm will be added to the protocol detailing the possibility that, if the investigators see no difference between the lower and the higher dose in terms of the wall function, the clinical trial could be scaled down to focus on the lower dose.

- Language will be added to the informed consent document that explains that any complication associated with the LVAD or related procedures would immediately put the participant into a “1A”

category, which means the participant would need to be transplanted within 15 days so as not to compromise survival.

- The investigators agreed to amend the ICD to include a statement about the potential risk of arrhythmias and the experimental nature of the protocol.

- Dr. London noted that there is a block on the needle that only allows 5 millimeters of penetration into the thick ventricular muscle so there should be no significant risk of perforation of the heart.

E. Public Comment

Kristina C. Borror, Ph.D., NIH Office for Human Research Protections, noted that the language in the informed consent document is complex and includes many typographical errors and much confusing wording. She recommended that an editor proofread the document.

Joseph Rokovich, Ph.D., Edwards Life Sciences, LLC, asked how participation in the trial would impact later transplantation, particularly if an AE were to occur. The investigators responded that participants with LVAD always see transplantation as the ultimate goal. Any complications associated with LVAD will put the subjects into a category to receive transplantation within 15 days.

F. RAC Recommendations

Dr. Wara summarized the following RAC recommendations:

- To more fully understand the potential for inadvertent germline transmission, consider assessing the risk of vertical transmission by sampling semen for the presence of AAV6.

- The canine preclinical animal studies are important for several reasons but in particular because it is a good model of human heart failure. These studies should be conducted to provide cardiac safety data before starting the clinical trial.

- The current study design calls for a fixed dose to be used. Since it will be difficult to determine the maximal tolerated dose or dose limiting toxicities with a fixed dose, consider modifying the design of the study by employing a dose escalation design that would more precisely define the maximal tolerated dose or dose limiting toxicity.

- Because of the heterogeneity within the myocardium, the response to injections may vary with the site of injection. Consideration should be given to randomizing the doses by injection site to minimize a bias due to this heterogeneity.

- The size of the study cohort should be reassessed and justified to assure the study's ability to detect toxicities and allow meaningful analyses and monitoring. A biostatistician should be consulted in carrying out this reassessment.

- Safety endpoints and stopping rules for this study should be defined in the protocol a priori. In addition, an algorithm displaying options to be taken in response to safety findings may be helpful in guiding the conduct of the study as well as the analysis of safety data by the Data and Safety Monitoring Board.

- The informed consent document should use simple, understandable language and avoid terms such as "therapy" and "generate new healthy heart cells", which could mislead subjects into thinking that the experimental product is a proven therapy. In addition, the document needs to be copy-edited to correct numerous typographical errors.

G. Committee Motion 2

It was moved by Dr. Lo and seconded by Dr. Childress that the above recommendations be included in the letter to the principal investigator (PI) and the sponsor as expressing the comments and concerns of the RAC; RAC members were reminded that they were voting on the issues raised, not on the specific wording of the recommendations. The vote was 13 in favor, 0 opposed, 0 abstentions, and 3 recusals.

V. Introduction to Upcoming Safety Symposium: Safety Considerations in Recombinant DNA Research with Pathogenic Viruses

Speakers: Kanta Subbarao, M.D., M.P.H., NIAID; Maria Cristina Cassetti, Ph.D., NIAID; and Marina O'Reilly, Ph.D., OBA

The 1 ½-day safety symposium will be held in conjunction with the September 2004 RAC meeting. The symposium will focus on the biosafety considerations associated with recombinant research with pathogenic viruses. Recent advances in recombinant DNA techniques have made it easier to generate certain types of recombinant viruses. Reverse genetics techniques allow for the generation of negative stranded RNA viruses from cloned DNAs. Using the technique, it is possible to generate recombinant viruses containing genes from different viral strains or to create mutations in individual genes. As case studies, the symposium will review research involving the 1918 influenza virus, highly pathogenic avian influenza viruses, and the coronavirus that causes severe acute respiratory syndrome (SARS- CoV).

The issues regarding risk assessment and appropriate containment for these types of experiments will be discussed at the safety symposium. The major goal of the symposium will be to develop a points to consider document to assist institutional biosafety committees (IBC) that review this research. Currently, the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, and the *Biosafety in Microbiological and Biomedical Laboratories* (fourth edition) (*BMBL*) provide some guidance and recommend biosafety level 2 for influenza virus research. To prepare for the symposium, a steering committee has been assembled consisting of several RAC members (Drs. Barkley, DeLuca, L. Johnson, and P. Johnson; Ms. Kwan; and Drs. Powers and Rosenberg) and several *ad hoc* experts. The mission of the steering committee is to review the agenda and recommend presentations, recommend panelists for discussion sessions, and frame questions to lead the discussion that will provide useful points to consider for IBCs.

Dr. Subbarao provided a background summary of influenza virology. Influenza A and B are enveloped viruses containing a single stranded negative sense RNA genome with eight segments expressing at least ten proteins. The envelope glycoproteins, hemagglutinin (H) and neuraminidase (N), are the immune targets and exist in multiple subtypes. In the last century, there have been three pandemics: 1918 caused by a H1N1 virus, 1957 caused by H2N2, and 1968 caused by H2N3. Water fowl and shore birds are reservoirs for influenza A viruses. Avian viruses and human viruses can reassort their eight segments to create novel viral strains. Highly pathogenic avian influenza (HPAI) outbreaks occur in poultry and some strains can also infect humans. H5, H9, and H7 viruses have infected humans. The H5N1 virus can directly infect humans from birds and has caused deaths during outbreaks in 1997, 2003 and 2004. Massive culling of infected poultry has controlled viral spread, but HPAIs remain a potential source of the next pandemic.

Because influenza viruses can alter their sequence and antibody binding ability, new epidemics occur each year and new vaccines need to be developed. The influenza RNA polymerase does not have a proofreading function, causing mutations to accumulate in the H protein preventing neutralization by anti-H antibodies from previous infections. Vaccines can be created by reverse genetics or reassortment of the H and N gene containing segments from a virulent virus with the six internal segments from an attenuated vaccine strain. Dr. Subbarao is working to generate candidate vaccines against HPAI, and study pathogenicity in animal models.

Her lab also develops animal models for SARS to test candidate vaccines. Virus replication models have been developed in mice, hamsters, and monkeys and it has been determined that antibodies from a

primary infection provides protection from subsequent challenges. Five candidate vaccines and three sources of monoclonal antibodies have been studied.

Dr. Cassetti provided an overview of NIAID-supported extramural research on recombinant influenza viruses. The DMID influenza program currently supports about 60 active grants, the majority of which aim to investigate the basic biology of the virus. Recently, NIAID has awarded several grants to support applied research into the development of diagnostic tools, antiviral drugs and vaccines. Reverse genetic techniques have accelerated the progress of research. For example, Dr. Kawaoka's group at the University of Wisconsin has used reverse genetics to create recombinant viruses expressing genes from pathogenic viruses in attenuated strains and determined that the a single amino acid change in the PB2 gene, one of the subunits of the viral polymerase, is associated with high lethality. Dr. Webster's group at St. Jude Children's Research Hospital determined that virulent viruses have an NS1 gene that allows the virus to bypass the host immune response. NIAID is also supporting research to determine the sequence of the 1918 influenza virus. Dr. Palese's group at Mt. Sinai School of Medicine has created recombinant viruses expressing up to five 1918 virus genes and determined that virulence was associated with the H, N and partially the matrix gene.

The rapid research progress raised associated biosafety issues. The BMBL was last updated before the common use of reverse genetics, and it recommends research with influenza virus at biosafety level 2. In 2001, NIAID organized a reverse genetics workshop that recommended risk assessments continue to be performed by IBCs, and that the BMBL be updated. NIAID has requested the assistance of OBA and the RAC to discuss containment and risk assessment for this type of research.

VI. Discussion of Human Gene Transfer Protocol #0403-633: A Phase I Trial of Immunotherapy with BHT-3009 Alone or Combined with Atorvastatin in Patients with Multiple Sclerosis

Principal Investigator:	Timothy L. Vollmer, M.D., St. Joseph's Hospital and Medical Center
Additional Presenters:	Frank H. Valone, M.D., Bayhill Therapeutics; Stephanie Broome, Ph.D., Bayhill Therapeutics; Mark W. Schwartz, Ph.D., Bayhill Therapeutics; Lawrence Steinman, M.D., Stanford University
Sponsor:	Bayhill Therapeutics
RAC Reviewers:	Drs. Bohn, DeLuca, Muzyczka, and Powers
Ad hoc Reviewer:	Stephen D. Miller, Ph.D., Northwestern University *(written response read into the record by Dr. Bohn)*

A. Protocol Summary

Multiple sclerosis (MS) is the most common nontraumatic cause of disability in young adults. In the United States, an estimated 350,000 people are affected by this disease, at a national annual cost of nearly $10 billion. BHT-3009 is an antigen-specific, immunotherapeutic agent currently in development as a potential treatment of relapsing-remitting MS. The product is designed to reduce levels of immune cells that target myelin basic protein (MBP), one of the main self-antigens in MS. BHT-3009 is a plasmid expression vector that encodes full-length human MBP. When BHT-3009 is administered by intramuscular (IM) injection, low-level expression of MBP occurs for a period of 2 to 4 weeks at the injection site and also within cells that traffic to draining lymph nodes. This limited expression of a self-antigen in a novel tissue context has been found to limit ongoing autoimmune responses in mouse and rat models of experimental autoimmune encephalomyelitis (EAE), the preclinical model for MS.

In studies of a mouse model of EAE, plasmid DNA expression vectors encoding a myelin autoantigen significantly reduced the severity of EAE disease and the frequency of relapses. Experimental treatment reduced the numbers of myelin antigen-reactive immune cells in animals with EAE. Recent studies by several laboratories suggest that atorvastatin and other members of this class of drugs, collectively known as statins, may have anti-inflammatory properties that may be beneficial in treating MS. In the mouse model of EAE, atorvastatin contributed to responses to an expression vector encoding a myelin autoantigen. Combination therapy significantly reduced average disability scores compared with control groups.

The proposed study is a multicenter, randomized, double-blind, dose-escalation, placebo-controlled trial to evaluate the safety of immunotherapy with BHT-3009 when given alone or when combined with atorvastatin in individuals with MS. Three dose levels will be administered, with 10 research participants being dosed at each level. Participants will be randomized to receive BHT-3009 plus atorvastatin, BHT-3009 plus atorvastatin-placebo, or BHT-placebo plus atorvastatin-placebo. During 13 weeks, participants will receive four IM injections of BHT-3009 or BHT-placebo and take two atorvastatin or atorvastatin-placebo tablets daily. After dosing and followup evaluations are completed, the study will be unblinded, and participants who had received placebo will be rerandomized to a dosing with BHT-3009 alone or to a dosing with BHT-3009 plus atorvastatin for an additional 13-weeks. Thus, all participants in the study will receive dosing with BHT-3009.

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

Eleven RAC members recommended in-depth review and public discussion of the protocol. The protocol will be the first use of a clinical gene transfer approach for MS. RAC reviewers Drs. Bohn, DeLuca, Muzyczka, and Powers and *ad hoc* reviewer Dr. Miller submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Bohn noted that efficacy studies have not been conducted using the actual product (BHT-3009) because of a lack of an appropriate animal model. She suggested that histopathology studies should include a careful analysis of possible effects on myelin of the peripheral and central nervous systems. If an immune response to the product leads to increased autoimmunity, the investigators should clarify how they would distinguish between this and spontaneous relapse. Although likely to be reviewed carefully by the DSMB, more information is needed regarding the determination of whether each dose is safe. The goals to explore markers of MS should be described specifically. The nature of the fine white precipitate in the product, although acceptable to FDA reviewers, should be specified. Participants might develop hypersensitivity to the product, leading to an anaphylactic response. The investigators should state how they will determine—and how many participants are necessary to decide—whether to go forward with the vector with and without statin. She also noted that the inclusion of placebo research participants is a strength of this proposal,

Dr. DeLuca stated that his main concern about the protocol is whether immunization will potentiate the autoimmune response, which result in a worsening of symptoms or induce tolerance, thereby reducing symptoms. The former scenario is briefly mentioned in the protocol as a safety issue. The PI should discuss the reasoning and preclinical data that support their assertion that this intervention will induce tolerance. He also wondered whether it is possible that, at some doses of antigen, potentiation of the autoimmunity will occur while at other doses, tolerance will be induced. Dr. DeLuca requested that the investigators discuss how the outcome of the preclinical experiments in the EAE mouse relate to the proposed clinical study and whether higher doses (with and without atorvastatin) have been tried in the mouse EAE model.

Dr. Muzyczka noted that the nonhuman animal models used to support the therapeutic effect of atorvastatin, combined with immunization to MBP via plasmid DNA, are not entirely appropriate models, thus making the efficacy data difficult to interpret. It is possible that the disease would be exacerbated by immunizing against the primary antigen for MS. He asked for further clarification about why the investigators are proposing a combination regimen and expressed concern about whether the investigators would have enough statistical power to determine whether there were any meaningful adverse effects at the end of the trial.

Dr. Powers noted that the informed consent document indicates that the risks associated with BHT-3009 in humans are unknown, but he suggested that there might be potential risks identified in nonhuman animal models that might be relevant to disclose. The informed consent document also should disclose any known and describable risks associated with termination of standard therapy, since the protocol appears to call for substitution of the experimental agent for the standard therapy. Dr. Powers also suggested that more specific criteria or clinical indicators be used for participant selection, in part

because the risk-benefit calculation is likely to vary depending on individual differences in the severity of the disease.

Dr. Miller noted that, overall, there are many more reasons not to proceed with this proposed human trial than there are reasons to go forward. He expressed concern that the EAE data were presented in a nonstandard fashion, making it difficult to evaluate efficacy in the mouse model. Dr. Miller noted that effectiveness in the mouse studies was established by sharp cutoffs, making problematic the establishment of the human dosing and timing regimens. He also noted concern about the safety issues related to treating MS patients with a DNA vaccine encoding a myelin protein that will be given by an immunogenic route. Dr. Miller also questioned whether the proposed immunologic assays would be sensitive enough to determine whether tolerance to MBP epitopes was induced.

C. RAC Discussion

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

- Dr. L. Johnson requested a clear rationale for using atorvastatin and asked whether it had been used clinically to treat MS. He also asked for clarification of the dosing regimen.

- Dr. Simari requested clarification about how the investigators use the mouse dose to determine the doses for the nonhuman primate and then for humans, for both the statin and the plasmid.

- Dr. DeMets asked when the monitoring committee would review the data—during the course of the trial or after the results for the 10 participants become available.

D. Investigator Response

Dr. Valone and colleagues responded with the following information:

- The use of statins in MS goes back about 7 years and is based on previous research conducted by other investigators, which showed that statins have the ability to decrease the inflammatory processes in the brain. In addition, other researchers have demonstrated that statins tend to inhibit the T-cell helper type 1 arm of the immune system in the development of new immune responses and tends to promote the T-cell helper type 2 (Th2) arm. Two goals in using a statin are to increase opportunities to prevent inadvertent activation of disease and to accelerate development of the Th2 response, which may be beneficial in the long term.

- MS patients have been exposed to statins, both informally and formally. About 15 percent of the MS population is taking statins at any given time. From a safety standpoint, the investigators do not expect that adverse effects will occur. The results of a Phase IIb trial with simvastatin (equivalent to atorvastatin) at 80 milligrams a day were reported at the American Academy of Neurology meeting in 2003; the investigators showed about a 43 percent reduction in disease activity as measured by magnetic resonance imaging (MRI), and no untoward reactions were seen in those participants.

- The rationale for the minimally effective dose was worked out first in the mouse models, ranging from about 2 micrograms up to 10 to 50 micrograms per mouse per dose with repeat dosing. In the clinic, results with plasmid DNAs show a minimal response at about 100 to 500 micrograms of plasmid, and responses generally increase with increasing doses.

- The trial is structured such that one month after all 10 participants in a dose cohort have completed their experimental dosing and their followup evaluation, the relevant data will be assembled, unblinded, and then reviewed by the DSMB. That cohort will consist of six participants who will have received the experimental drug and four who will have received placebo. Also this trial is set up so that real-time data is available and safety reports will be available to the DSMB online within 24 hours of receipt.

- The investigators explained that BHT-3009 is designed to modulate the immune response to MBP. Clinical experience in the treatment of MS patients with MBP protein and peptides and Bayhill's preclinical data indicate that treatment with BHT-3009 is more likely to induce tolerance than to potentiate autoimmunity.

E. Public Comment

Dr. Borror stated that "therapeutic" language—the use of the words "therapy," "treated," "treatment," and "patients"—should be changed. In addition, a definition of lumbar puncture and its associated risks should be added to the informed consent document, and the wording of the risks for atorvastatin should be simplified.

F. RAC Recommendations

Dr. Wara summarized the following RAC recommendations:

Because the pathogenesis of multiple sclerosis (MS) is not fully understood, the role of the experimental product, BHT-3009, in the treatment of MS remains speculative and will have to be empirically determined. In addition, the assessment of the risks and benefits of BHT-3009 is difficult due to the variability and unpredictability of spontaneous relapses.

- As such, the proposed number of subjects should be reassessed to assure that adequate statistical power will be present to detect toxicities associated with administration of BHT-3009.

- The identification of endpoints to be monitored by the DSMB and the frequency and timing of its data reviews should be more clearly described.

- The informed consent document should describe in simple, easily understood language the disease markers chosen as endpoints that will define toxicities associated with BHT-3009, the risks associated with lumbar puncture, and the risks associated with the use of atorvastatin.

G. Committee Motion 3

It was moved by Dr. Bohn and seconded by Dr. Heslop that the above recommendations be included in the letter to the PI and the sponsor as expressing the comments and concerns of the RAC. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VII. Discussion of Human Gene Transfer Protocol #0404-641: A Phase 1, Open-Label, Nonrandomized, Dose-Escalation, Multicenter Therapeutic Trial of the Safety, Immunogenicity, and Efficacy of GI-4000, an Inactivated Recombinant *Saccharomyces cerevisiae* Immunotherapeutic Expressing Three Different Mutations of the Ras Oncoprotein, in Patients with Solid Tumors Expressing Mutations in Ras

Principal Investigator:	Bert O'Neil, M.D., University of North Carolina School of Medicine, and Timothy C. Rodell, M.D., GlobeImmune, Inc.
Additional Presenters:	Richard C. Duke, Ph.D., Alex Franzusoff, Ph.D., and John Ferraro, GlobeImmune, Inc.
Sponsor:	GlobeImmune, Inc.
RAC Reviewers:	Drs. Barkley and DeLuca and Ms. Kwan

Drs. Linial and L. Johnson recused themselves from the discussion of this protocol.

A. Protocol Summary

Many human cancers have been shown to have mutations in proteins that control cell growth and division—mutations that are required for the involved cell to become a cancer. Mutations in human *ras* genes and their encoded Ras oncoproteins have been implicated in the pathogenesis of multiple solid tumors, including pancreatic, colorectal, non-small cell lung cancer, ovarian cancer, and melanoma. The most common mutations in *ras* occur at codons 12, 13, and 61, all three of which result in constitutive activation of the Ras/epidermal growth factor receptor (EGFR) pathway resulting in uncontrolled cell division. Because these mutations are not random, but are required for carcinogenesis, these mutated oncoproteins represent ideal targets for cancer immunotherapy.

Globelmmune has developed a series of yeast *(Saccharomyces cerevisiae)* based mutated Ras immunotherapy products targeting these common mutations and has demonstrated in non-clinical models that these immunotherapeutic agents block the growth of tumors expressing mutations at the target positions in an antigen-specific fashion. Yeast are efficiently taken up by dendritic cells, resulting in an enhanced cell-mediated immune response directed at cancer cells expressing mutant Ras protein. The GI-4000 series of Ras products is made up of three different immunotherapeutics, each of which carries the two most common mutated amino acid substitutions at the 61 position and one of the three most common mutations at the 12 position. These products have been tested in nonclinical safety studies in animals and been found to have minimal toxicity, generally limited to injection site reactions.

The investigators propose conducting a multisite clinical trial in cancer patients, injecting GI-4000 under the skin of research participants whose cancers have been shown to be making the mutant Ras protein. The cancer patients will be monitored for toxic effects, Ras-specific immune responses, and any therapeutic benefits related to the injection of GI-4000.

B. Written Reviews by RAC Members

Sixteen RAC members recommended in-depth review and public discussion of the protocol. The protocol involves the novel use of a yeast-based gene delivery system, a new strategy of using mutated and truncated Ras oncoproteins for tumor immunotherapy, and the first use of this construct both in humans and in nonhuman primates. RAC reviewers Drs. Barkley and DeLuca and Ms. Kwan submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Barkley expressed concern about several issues related to the informed consent document, including the need to describe the potential risks to participants of biopsies, and withholding medication prior to the skin tests your yeast sensitivity. There is also a need for discussion of delaying subsequent chemotherapy, which might compromise overall treatment. Dr. Barkley requested to see more definitive studies showing that yeast cells are killed by the inactivation process. He requested a comparison of data from preclinical animal studies using GI-4000 vaccination with preclinical data from similar animal studies evaluating other experimental cancer immunotherapies. Dr. Barkley asked the investigators whether maintaining quality control would be more difficult if there were fewer than three participants at each site and suggested that a minimum acceptable number of participants to be enrolled at each site be set.

Given that this is the first protocol using yeast and there is little information available regarding the potential consequences of repeated administration of yeast to humans, Dr. DeLuca suggested that the yeast should be quantitatively inactivated. An inactivation curve should be generated and provided. One inclusion criterion is an analysis of potential participants' tumor tissues to reveal the presence of one of the *ras* alleles represented in the vaccine; however, he questioned whether some of these cancers could possess germline mutations in *ras* rather than acquired mutations. Tumors with germline mutations may not be expected to respond to the introduced immunogen. Dr. DeLuca suggested that, if germline mutations are possible, the investigators should consider screening for and excluding such potential participants.

Regarding the informed consent document, Ms. Kwan noted that the language used appears to be reasonable but may exceed the reading level of some potential participants. She suggested consulting local educators. The informed consent document also should include a notation about whether the

investigators or sponsoring institutions have any financial interest in the company. Neither an autopsy request nor a pregnancy test was included in the first draft of the informed consent document. She found confusing the references to GI-4000 as "a product." Ms. Kwan wondered whether there were statistical and/or clinical advantages to treating all three proposed products as one.

C. RAC Discussion

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

- Dr. Nemerow asked whether the investigators were concerned about selecting a subset of tumor cells that do not have the mutation, even though they will screen participants for presence of the exact mutation.

- Ms. Kwan asked for discussion about evidence that shows that the complement system is not activated by this product, because yeast *in vivo* could activate the complement system and thereby place participants in shock.

D. Investigator Response

Dr. Rodell and colleagues responded with the following information:

- The sponsor responded that it is not clear from the literature in other animals or humans how common low-frequency *ras* mutations are in individuals who have a predominant mutation in their tumor. Data from the mouse study suggest that it is not possible to ascertain whether the low-frequency mutations are being selected or whether the tumor is mutating beyond current ability to detect that mutation. As development of this process is refined, the investigators expect to be able to prevent selecting cells containing the low-frequency mutations.

- Germline mutations in *ras* have not been reported in the literature. Since acquired or introduced mutations in *ras* are sufficient for tumorigenesis, the prediction would be that germline mutations might cause cancer prenatally or neonatally. Bases on numerous studies of mutant Ras protein in the tumor cells of patients with different cancer types, only tumor cells or precancerous cells are anticipated to have mutations in ras.

- The Investigators agree to share with the RAC more information about the yeast inactivation process. The release test to be used is the *U.S. Pharmacopeia* (*USP*) standard test used for sterile pharmaceuticals. Forty vials of product are inoculated according to *USP* standards, tested in rich media, and evaluated for 2 weeks to determine whether there is growth of any organism, including yeast.

- The informed consent document will be modified to define more clearly GI-4000 as three separate products.

- A degree of complement activation adequate to cause shock or any systemic response would have been detected in clinical signs in the toxicity studies, assuming that the test species in the toxicity studies adequately predicted what would occur in humans. The yeast cell wall has been shown to activate complement, however there are no published data indicating that effect from whole yeast. The literature indicates that the doses of yeast cell wall required for systemic complement activation are at least 1,000-fold and may be 10,000-fold less than what is proposed for this clinical trial. Even given that information, the investigators have added an assay at the first visit that will check for activation of complement after 30 or 60 minutes, the time at which the investigators' consultants indicate that maximum activation will occur.

E. Public Comment

No comments were received from the public.

F. RAC Recommendations

Dr. Wara summarized the following RAC recommendations:

- This protocol is the first use of yeast as an immunotherapeutic agent in humans; therefore, the yeast heat inactivation process should be optimized to ensure safety for the research participants.
    - In order to assure that the yeast heat inactivation is complete, as measured by the GlobeImmune in-house procedure, consideration should be given to generating a heat treatment survival curve for yeast at 56° C for up to one hour. The RAC is interested in receiving the details of this study and information about specific methodology, such as steps to eliminate the potential that buffers or other constituents of the preparation would mask the presence of viable yeast cells.

- To assure appropriate enrollment across all potential subject populations at all trial sites (12-2 subjects at up to six research centers), consideration should be given to revising the protocol, which as currently written, may limit the number of subjects to as few as one subject at several sites.

- Consider revising line 1 of section 11.3 of the protocol, which is unnecessarily apologetic since the statistics section appears to be accurate and appropriate.

- The RAC recommends the following modifications and additions to the informed consent document:

    - Describe the risk associated with biopsy, even though it might not be necessary for all research participants.
    - The informed consent document should use simple, understandable language and should attempt to be written at an eighth grade reading level. The investigators should consider contacting reading experts at local schools to assist with adjusting the reading level of the document.
    - Include information regarding any real or apparent conflict of interest for the investigators.

G. Committee Motion 4

It was moved by Dr. Gelehrter and seconded by Dr. Barkley that the above recommendations be included in the letter to the PI and the sponsor as expressing the comments and concerns of the RAC. The vote was 13 in favor, 0 opposed, 0 abstentions, and 2 recusals.

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

Presenters: Drs. DeMets and Lo and Cheryl McDonald, M.D., NIH OBA

Dr. DeMets distributed a first draft of design principles that any protocol should consider—the basics that often are lacking in protocols reviewed by the RAC. Based on this document, two summer interns (one with Dr. Lo and one with Dr. McDonald) will review the gene transfer protocols examined by the RAC during the past 2 years. This review will look at a number of features and basic design elements of the clinical trials to determine to what extent RAC comments were responded to and whether a problem exists in trial design. The next step is to obtain the data from those protocols; the summer interns are preparing to start that work, which should be completed by the end of the summer. Dr. DeMets noted that there will be an update on this project, particularly on the work done by the summer interns, at September 2004 RAC meeting.

IX. Day One Adjournment/Dr. Wara

Dr. Wara adjourned the first day of the June 2004 RAC meeting at 4:30 p.m. on June 8, 2004.

X. Day Two Opening/Dr. Wara

Dr. Wara opened the second day of the March 2004 RAC meeting at 9:00 a.m. on June 9, 2004.

XI. Presentation of NIH Award of Merit to Dr. James Childress, Dr. Larry Johnson, Dr. Maxine Linial, and Dr. David Sidransky/Dr. Amy P. Patterson, OBA Director

Dr. Patterson expressed the gratitude of the NIH and the OBA to Drs. Childress, L. Johnson, Linial, and Sidransky for their service on the RAC, and presented them with certificates. She also noted the departure of Dr. Alexander Rakowsky, senior medical officer at the OBA, who will be taking the position of director of regulatory affairs at Columbus Children's, part of the Ohio State University Medical Center**.**

XII. Data Management Report/Drs. L. Johnson, Simari, and Wara

Dr. Simari reported that there had been 18 protocol submissions since March 2004, 13 of which were not selected for public review. Of the 13 protocols not selected for public review, 10 were for cancer, 1 was for cardiovascular disease, 1 was for diabetic neuropathy, and 1 was for HIV infection. The vector systems to be used included six pox vectors, two plasmid vectors, and three retroviral vectors, including a lentiviral vector.

The OBA tabulated data and provided background information on the 132 AEs reported to the OBA in the previous quarter. Sixteen events were reviewed in detail; seven were classified as new "type A" events, meaning that they were considered to be "serious, unexpected, and possibly related to the investigational agent." Dr. Simari stated that the RAC reviewers determined that none of the events warranted further public discussion at this time.

Dr. Wara reported that 59 annual updates and 32 protocol amendments submitted to OBA in the past 3 months. Of the 32 amendments, 20 were for study site or PI changes. Of the remaining 12 amendments, only two warranted public discussion: #9908-337 for adenosine deaminase (ADA)-deficient severe combined immunodeficiency disease (SCID), and #0302-571, for non-small cell lung cancer (NSCLC).

Protocol #9908-337 involves transduction of CD34-positive cells from the umbilical cord blood of infants or the bone marrow of children with ADA-deficient SCID and is amended to increase the likelihood of transferred cell survival. Polyethylene-glycol-ADA will be discontinued prior to infusing the transduced CD34-positive cells, and all participants will receive one round of moderate-dose busulfan to allow for bone marrow cytoreduction. Both changes are based on preliminary success reported by Claudio Bordignon, M.D., and colleagues in Italy in a similar study to the proposed study. The newly amended protocol will enroll six additional participants. This study includes a well-developed section detailing the potential risks associated with the protocol changes as well as defined stopping rules.

Protocol #0302-571 is a Phase II randomized study of a granulocyte-macrophage colony-stimulating factor (GM-CSF), gene-modified autologous tumor vaccine, CG8123, with and without low-dose cyclophosphamide in advanced-stage NSCLC. This protocol is amended to address three reported serious AEs—all deaths—in previously enrolled participants. The deaths were determined likely to be related to tumor harvest for the direct purposes of the protocol, and therefore, the study has been revised in three areas: (1) The eligibility criteria for tumor procurement were substantially modified to exclude participants with comorbidities that might lead to operative complications; (2) tumor procurement will be limited to minor surgical procedures (including lymph node or soft-tissue-mass sites) and will not include open, substantial surgical procedures; and (3) the stopping rules have been redefined to include deaths related to the tumor-harvest procedure. Of the first 40 participants enrolled, 3 died because of the surgical tumor-harvest procedure. In accordance with the new stopping rule, if one more death occurs by the time participant #60 has received the vaccine or if two more deaths occur by the time participant #90

has received the vaccine, the study will be stopped until the data are reviewed and discussed with the appropriate regulatory bodies.

XIII. Discussion of Human Gene Transfer Protocol #0404-638: A Phase I Trial of Intramuscular Injection of a Recombinant Adeno-Associated Virus 1-Alpha 1-Antitrypsin (rAAV1-CB-hAAT) Gene Vector to AAT-Deficient Adults

Principal Investigators:	Terence R. Flotte, M.D., and Mark L. Brantly, M.D., University of Florida
Additional Presenters:	Barry J. Byrne, M.D., Ph.D., and Margaret Humphries, R.N., University of Florida; Sue Washer and Paula Wilkerson, Applied Genetic Technologies Corporation
Sponsor:	Applied Genetic Technologies Corporation
RAC Reviewers:	Drs. Childress, Gelehrter, and L. Johnson

Dr. Muzyczka recused himself from the discussion of this protocol.

A. Protocol Summary

Alpha1-antitrypsin (AAT) is a serum protein that is normally produced in the hepatocytes within the liver. Individuals with abnormalities in AAT levels are at risk for lung disease, and those with a total absence of AAT expression are prone to emphysema. The accumulation of mutant AAT protein in hepatocytes results in clinical liver disease. Approximately 63 percent of AAT-deficient individuals will have obstructive pulmonary disease as a diagnosis at the time of death. Protein replacement therapy is available for prevention of the progression of lung disease due to AAT deficiency and consists of weekly repeated intravenous (IV) infusions of human AAT.

The investigators propose to perform a study to test rAAV-hAAT, an adeno-associated virus-derived vector expressing AAT. In this study, participants will receive three doses of the vector. Different tests then will be conducted on the participants' blood and breathing to determine safety and efficacy. Any participants currently on AAT replacement therapy will discontinue that therapy for 4 weeks prior to receiving their vector dose in the clinical trial and will resume that therapy 11 weeks after the experimental dose has been administered.

B. Written Reviews by RAC Members

Three RAC members recommended in-depth review and public discussion of the protocol. The protocol involves the first use in humans of adeno-associated virus serotype 1 (AAV1) that may have a different biodistribution than the previously studied AAV2 vectors. Murine studies suggest that the vector is disseminated beyond blood and to gonads following IM injection; other biodistribution studies of AAV1 are in progress. In addition, replacement therapy with recombinant AAT protein is available and effective, although less desirable. RAC reviewers Drs. Childress, Gelehrter, and L. Johnson submitted written reviews, to which the investigators responded in writing and during this meeting.

Noting that the protocol and informed consent document in general were clear and straightforward, Dr. Childress concentrated his review on the informed consent document and process. The informed consent document is long and complex but free of jargon and clearly written, with the exception of the Health Insurance Portability and Accountability Act (HIPAA) language, which could be clarified. Different numbers of potential research participants are used in different places in the protocol. Dr. Childress noted that the discussion of therapeutic alternatives was limited; rather than being a substantial part of the document, the wording states only that "the research doctor will discuss this with you." Dr. Childress suggested that the emphasis be placed on a discussion with the participant's own doctor and that additional discussion occur in the document regarding a "decision monitor," who will contact the potential participant to discuss the pros and cons of participating in this trial.

Dr. Gelehrter asked for an explanation of why AAV1 would be used in this protocol instead of AAV2, which has been used in previous clinical trials. He expressed concern about gonadal expression and expression in sperm and requested an explanation of why preclinical studies have looked at expression in sperm at 2 weeks when sperm stays in the epididymis 60 to 90 days.

Dr. L. Johnson noted two issues related to the informed consent document: the rationale for reinstituting hAAT on day 75 as opposed to an earlier or later time needs to be explained and disclosure of any financial relationship between Drs. Flotte and Byrne and Applied Genetic Technologies Corporation (AGTC) should be stated clearly. He requested further information regarding the rationale for the current study, the efficacy of weekly protein infusion of hAAT, and the choice of promoter—whether the investigators had considered using elongation factor-1 alpha for expression of AAT in mice. He also requested more information about the consequences of expression of hAAT in the brain—IM administration of the study vector at high doses has led to the detection of greater than 100 copies of vector DNA within the gonads of mice for more than 90 days, and AAV1 DNA also has been detected in murine brain at higher doses for periods of up to 90 days; and injection site inflammation—its expected duration and what has been learned about this inflammation from an ongoing AAV2 clinical trial.

C. RAC Discussion

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

- Dr. DeMets requested that the protocol state the extent to which the National Heart, Lung, and Blood Institute (NHLBI) will be involved in monitoring.

- Dr. Lo asked whether the investigators' consulting radiologist recommended using MRI rather than computerized tomography (CT) to rule out any clinically apparent problem with participants' arms, before injection.

- Dr. Simari requested feedback for the RAC about how the investigators moved from the first study to this study, the role of the NIH in that development, and how development has been hastened or hindered by regulatory issues.

D. Investigator Response

Dr. Flotte and colleagues responded with the following information:

- The NHLBI first funded this research as part of a program project grant in 1997. After the first 5 years, the investigators switched to an independent R01 mechanism, primarily because, in a program project grant mechanism, it is difficult to include a clinical protocol because funds are not released until institutional review board approval is completed. If a clinical protocol is included as anything other than a future direction, all funding is held until the FDA releases the protocol from clinical hold, the investigational new drug application is filed, the RAC has reviewed the protocol, and so forth. Therefore, it is somewhat challenging to get the timing just right to obtain NIH funds and be ready to do a clinical protocol. However, the NHLBI funding took this research through the proof of concept into the early preclinical toxicology work. Had the investigators not had the institutional investment of several million dollars, there would have been a major timelag before the company started up and received the full capital investment capable of continuing product development.

- The NHLBI has yet to state definitively that it will participate as the DSMB in this protocol. There are two reasons why the NHLBI DSMB is the best choice: (1) The NHLBI is monitoring the current (similar) study, and (2) because of potential conflicts, any DSMB constituted either by the university or by AGTC is potentially biased and the NHBLI DSMB will not have that problem.

- For the purposes of the investigators, either CT or MRI would be appropriate. CT is less expensive and is a gross screening procedure. The investigators have discussed this issue and may further consider it before the study begins.

- The rationale for obtaining a later time point semen sample is that, in the nonhuman animal models, vector DNA is detected first in the gonads and later in the semen. If vector DNA is detected in semen, even if not detected in motile sperm, the investigators will continue to monitor participants past the usual 90 days.

E. Public Comment

Dr. Borror noted that every page of the informed consent document included a line or two with improper spacing that made it difficult to read. Some words included in the document are not commonly understood and should be defined (e.g., "genomes," "mid-arm circumference measurement"). In addition, the term "study agent" may be confusing, since "agent" generally is understood by the public to be a person.

Dr. Rakowsky asked the investigators to discuss obtaining a semen sample at a later time point.

F. RAC Recommendations

Dr. Wara summarized the following RAC recommendations:

- In order to more fully understand the potential for inadvertent germline transmission, consider conducting pre-clinical studies on vertical transmission using the AAV serotypes under development. Enrollment of subjects in the clinical protocol need not await the results of these studies, however.

- Because sperm may reside in the epididymis for an extended time, consider additional studies on semen collected in an interval between 30 and 60 days following the administration of the experimental product to assess whether AAV vector is present in motile sperm.

- The potential for significant injection site inflammation is a safety concern. As such, a specific definition of "dose-limiting toxicity" for injection site inflammation should be outlined in the protocol.
- The potential for significant injection site inflammation is a safety concern. As such, a specific definition of "dose-limiting toxicity" for injection site inflammation should be outlined in the protocol.

- The fact that a data and safety monitoring board will be organized to monitor data from the trial. It should be noted in the protocol and the board's specific functions and management should be described. Subjects should also be informed through the consent document that trial data will be monitored in this study.

- The investigators should reexamine the study's design to assess whether the currently proposed number of subjects is sufficient to adequately address the study endpoints.

- The informed consent document should make clear that subjects will not be required to resume AAT protein replacement therapy if their serum levels of AAT are in the therapeutic range on day 75 post-injection.

- There should be a more thorough discussion of therapeutic alternatives in the informed consent document. However, if this recommendation is not adopted, it will be important for the document to make it clear that the subjects should request information about alternatives to study participation from the investigators or their own healthcare provider.

- As written, the reading level of the informed consent is too complex (e.g., the term “genome” is not commonly understood) and consideration should be given to revising it so that it will be accessible to a general reader.

G. Committee Motion 5

It was moved by Dr. Powers and seconded by Dr. Childress that the above recommendations be included in the letter to the PIs and the sponsor as expressing the comments and concerns of the RAC. The vote was 15 in favor, 0 opposed, 0 abstentions, and 1 recusal.

XIV. Discussion of Human Gene Transfer Protocol #0404-643: A Phase I/II Dose-Escalation Trial of Intravesical CG0070 for Superficial Transitional Cell Carcinoma of the Bladder after Bacillus Calmette-Guerin Failure

Principal Investigators:	John Nemunaitis, M.D., US Oncology, Inc., and William A. See, M.D., Medical College of Wisconsin
Additional Presenters:	James Burke, M.D., Peter K. Working, Ph.D., and D.C. Yu, Ph.D., Cell Genesys, Inc.
Sponsor:	Cell Genesys, Inc.
RAC Reviewers:	Drs. Heslop, Lo, Nemerow, and Sidransky

A. Protocol Summary

Bladder cancer is the fourth most common cancer affecting men in the United States and the eighth most common cause of cancer in women. The majority of bladder cancers contain specific gene mutations, referred to as Rb-pathway defects, which cause the cell to grow without normal control, resulting in a cancer.

This study uses an adenoviral vector that has been genetically modified to kill cancer cells that contain growth control Rb-pathway defects. The vector was also modified to produce GM-CSF, which stimulates the immune system to destroy tumor cells. The concept behind this research is that potentially there will be an immune response both locally within the bladder and at distant sites (beyond the bladder) that will provide anti-tumor activity.

This experimental, modified vector, CG0070, will be delivered directly into the bladder one time in some research participants and every week for 6 weeks in other participants. In addition, a special detergent called DDM (dodecyl maltoside) will be used to wash the bladder prior to instillation of the CG0070 in an effort to improve virus uptake in the bladder.

The primary goal of this study is to assess the safety and establish the maximum-tolerated dose (MTD) or maximum feasible dose (MFD) in the single and multi-dose regimens of CG0070. Participants will actively participate in the study for approximately 2 years, and then they will be contacted periodically for up to 15 years.

B. Written Reviews by RAC Members

Twelve RAC members recommended in-depth review and public discussion of the protocol. The protocol involves novel, conditionally replicating, oncolytic adenoviral vector for early-stage disease of superficial transitional cell carcinoma of the bladder. The vector proposed for this study incorporates several novel features, including a combination of therapeutic genes and promoters to facilitate tumor cell-killing. RAC reviewers Drs. Heslop, Lo, Nemerow, and Sidransky submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Heslop requested additional information regarding the justification for starting at high-dose levels. She also requested preclinical data on treating the bladder with the DDM detergent as well as any data

using this detergent in combination with the oncolytic agent containing the GM-CSF transgene. Dr. Heslop wanted further explanation about why the investigators chose this patient population—people in early-stage disease following failed treatment with BCG.

Dr. Lo reviewed this protocol in three main arenas: possible AEs of the proposed intervention, statistical issues, and consent issues. AEs may be caused by the adenoviral vector, by expressed GM-CSF, or by the DDM enhancer; these factors may have additive or multiplicative effects on, for instance, liver function or coagulopathy. He asked whether nonhuman animal studies had been conducted for repeated intravesicular doses of all three interventions in combination, whether safety studies of the DDM detergent had been carried out after intravesical administration to humans, and whether there is any previous human experience with repeated administrations of intravesicular CG0070. Stopping rules need to be established based on the historical and predicted response rates. Dr. Lo suggested separating the informed consent document into three separate documents—one each for the Phase I single dose, the Phase I multiple dose, and the Phase II aspects of this study—and that information on safety from the prior phases be provided to the participants in the latter phases. The use of the term "drug" to refer to the investigational agent in this study should be changed to a more neutral term which doesn't confer an unrealistic expectation of clinical improvement.

Dr. Nemerow noted two main concerns: the high amount of vector proposed for the dose-escalation study and the lack of quantitative data showing preferential viral replication in transitional cell carcinoma (TCC) vs. normal tissue. In addition, he noted that the investigators provided little information on the vector biodistribution in nonhuman animal models or data on whether the primary adenoviral receptor or integrin coreceptors are adequately exposed on the surface of normal bladder or TCC *in vivo* before or after dosing with DDM. Dr. Nemerow also requested discussion from the investigators as to whether they are concerned about the potential toxic effects of GM-CSF delivered at the high doses of the adenoviral vector in the dose-escalation study. Noting that the investigators claim that $1x10^2$ viral particles are removed following the initial wash, he wondered how this number was determined and how much time would elapse between dosing and washing.

Dr. Sidransky's review of this protocol, which was read into the record by Dr. Heslop, included the following concerns:

- Regarding participant selection and inclusion criteria, Dr. Sidransky noted that other gene transfer studies have focused on participants who are not candidates for cystectomy or who are scheduled for cystectomy anyway. He requested more information about how the investigators will present the option of surgical therapy through cystectomy vs. this experimental Phase I study.

- With regard to the exclusion criteria, Dr. Sidransky noted that insufficient emphasis had been placed on the shedding of white or red blood cells into the urine; such individuals are likely to be more susceptible to systemic BCG toxicity, according to previous experience with erosive lesions in the bladder. This then suggests that it is possible that viremia could occur in such participants and this could lead to systemic toxicity.

- Reports of transient liver and anticoagulation abnormalities with direct IV injection for similar viruses are a concern that needs to be addressed.

- The dosing schedule is complicated; Dr. Sidransky suggested further discussion on the statistical basis for this regimen and approach.

- It would be worthwhile to assess every primary tumor for inactivation of the Rb pathway, minimally with p16 and pRb immunohistochemistry. Also, additional marker studies in the urine, including emerging molecular markers (e.g., LOH, promoter methylation) should be considered given the unique aspects of the study.

- Intratumoral injection models might not be relevant so using more relevant bladder tumor models in the preclinical studies might be more enlightening and predictive for this proposed clinical study.

Additionally, toxicity testing using both the DDM was and the virus together would be advisable in the preclinical testing.

C. RAC Discussion

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

- Dr. Larry Johnson requested further information about DDM. He commented on the extensive work done on intercellular junctions. He questioned the use of this enhancing agent and its potential effect on intercellular junctions that might allow increased permeability and penetration of the conditionally replicating vector into the bloodstream. Accordingly, Dr. Johnson sought assurance that there would be adequate monitoring (with PCR) for adenovirus for an extended period of time.

- Dr. Lo suggested that the informed consent document include information about potential financial arrangements between the sponsor and the researchers conducting the clinical trial and about whether the researchers have stock, options, or ownership in the sponsoring company.

- Dr. DeLuca noted that biodistribution and safety studies were conducted in an animal model in which adenovirus does not replicate, and the Ad vector proposed for this human study is a replicating virus. Because of this discrepancy, he requested more discussion of the attenuation of this virus.

- Dr. DeLuca asked whether the investigators had conducted studies to address whether, when propagating this virus or passing it on to cells where it should not replicate, forward mutations could occur that would allow the virus to grow independent of whether or not the cells are dividing.

D. Investigator Response

Drs. Nemunaitis and See and colleagues responded with the following information:

- Several dozen agents were studied to select one that could improve transduction with minimal disruption and long-term effects on the urothelium before the Investigators chose DDM as the enhancing agent. Animal biodistribution studies are being conducted using three time points out to 56 days and in several tissues, including the bladder, ureter, and kidneys

- In the proposed clinical study, data on vector biodistribution and shedding into the urine will be collected at early time points: the day of dosing, up to 6 hours after dosing, at 24 hours, 2 and 5 days after dosing each week the vector is administered in addition to a weekly collection of urine, blood, saliva, and feces on an ongoing basis. These collections will be assessed by PCR to determine how long the samples need to be collected for adequate monitoring.

- The Investigators noted that a very similar detergent has been used in intravesical instillations along with a replication defective Adp53 virus given at 7.5×10^{13} PFU dose without any significant peripheral toxicity.

    - The Investigators noted that compared to wild-type virus or other oncolytic viruses that have been given intravenously, this is a very attenuated virus. The participants in the research study will be monitored closely and if any toxic effects occur at lower doses, then the study dose may not be escalated up to the planned 10^{14} dose level.

E. Public Comment

Dr. Borror noted that the words “therapy” and “treatment” appeared throughout the informed consent document and she recommended the Investigators avoid such terms as they imply efficacy where none is yet proven.

F. RAC Recommendations

Dr. Wara summarized the following RAC recommendations:

- The use of the DDM detergent, which enhances the potential systemic delivery of the vector construct, and the use of an animal model that may not provide information about the potential of this vector to replicate in human non-malignant cells, raise safety concerns about proceeding to the human Phase I trial. The Investigators should strongly consider the use of appropriate bladder carcinoma/animal model to more precisely determine the does of conditionally replicating Ad/GM-CSF vectors required to 1.) achieve efficient initial infection and subsequent spread, and 2.) restrict tumor cell growth, and 3.) recruit antigen-presenting cells.

- Please reassess the clinical trial design and clarify that the Maximum Tolerated Dose (MTD) determined in the Phase I portion of the trial will inform the decision about the dose for the Phase II portion of the trial.

- Systemic levels of GM-CSF should be closely monitored and subjects should be closely followed for side effects of GM-CSF, such as capillary leak, considering the high doses of Ad/GM-CSF vectors proposed for this study.

- The inclusion criteria for enrollment require normal D-dimer levels. Please clarify whether subjects who have isolated elevations of D-dimer levels will be allowed to enroll.

- The exclusion criteria prohibit enrollment of participants with "clinically significant bleeding or hematuria within 6 weeks prior to study entry." Since the degree of hematuria may correlate with the degree of involvement of the malignancy in the bladder, and the consequent potential for adverse effects, please quantify, by red cell count, the degree of hematuria that will be set as an exclusion criterion.

- The informed consent document should use simple understandable language and avoid terms such as "treatment" or "therapeutic effects" that could mislead subjects into thinking that the experimental product is a proven therapy.

- The informed consent document should contain a comprehensive discussion of the treatment options available to patients with the disease under study so that prospective research participants can make a fully informed decision regarding participation in this study.

- The informed consent document should include information regarding the presence or absence of any Conflicts of Interest, such as financial relationships between the Investigators and the Sponsor.

- The informed consent document should contain language noting that proceeding to Phase II portion of the study is contingent upon successful completion of the Phase I portion of this study.

G. Committee Motion 6

It was moved by Dr. Heslop and seconded by Dr. Gelehrter that the above recommendations be included in the letter to the PIs and the sponsor as expressing the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

XV. Closing Remarks and Adjournment/Dr. Wara

Dr. Wara thanked the participants and adjourned the meeting at 12:35 p.m. on June 9, 2004.

_____

Stephen M. Rose, Ph.D.
Executive Secretary

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

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

Date:

_____

Diane W. Wara, M.D.
Chair

Attachment I
Recombinant DNA Advisory Committee Roster

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Attachment II
Public Attendees

Dale G. Ando, Cell Genesys, Inc.
Stephanie Broome, Bayhill Therapeutics
James Burke, Cell Genesys, Inc.
Reuben Cohen, VIRxSYS Corporation
Tonya Custalow, Sign Language Associates
Boro Dropulic, VIRxSYS Corporation
Richard C. Duke, GlobeImmune, Inc.
David Ennist, consultant to Cell Genesys, Inc.
John Ferraro, GlobeImmune, Inc.
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Hideki Garren, Bayhill Therapeutics
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Paula Wilkerson, Applied Genetic Technologies Corporation
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Xiao Xiao, University of Pittsburgh

DC Yu, Cell Genesys, Inc.
Yongjie Zhou, FDA

Attachment III
Abbreviations and Acronyms

AAT	Alpha1-antitrypsin
AAV	adeno-associated virus
AAV1	adeno-associated virus serotype 1
ADA	adenosine deaminase
AE	adverse event
AGTC	Applied Genetic Technologies Corporation
AIDS	acquired immunodeficiency syndrome
BCG	bacillus Calmette-Guerin
BMBL	*Biosafety in Microbiological and Biomedical Laboratories*
BSL	biosafety level
CT	computerized tomography
DDM	dodecyl maltoside
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
EAE	experimental autoimmune encephalomyelitis
FDA	U.S. Food and Drug Administration
GM-CSF	granulocyte-macrophage colony-stimulating factor
HIV	human immunodeficiency virus
IBC	institutional biosafety committee
IM	intramuscular
IV	intravenous
LVAD	left ventricular assist device
MBP	myelin basic protein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSCLC	non-small cell lung cancer
OBA	NIH Office of Biotechnology Activities
PCR	polymerase chain reaction
PI	principal investigator
RAC	Recombinant DNA Advisory Committee
rAAV1-CB-hAAT	recombinant adeno-associated virus 1-alpha 1-antitrypsin
SARS	severe acute respiratory syndrome
SCID	severe combined immunodeficiency disease
SERCA2a	sarcoplasmic reticulum calcium ATPase 2a
TCC	transitional cell carcinoma
Th2	T-cell helper type 2
USP	*U.S. Pharmacopeia*
VAD	ventricular assist device
VSVG	vesicular stomatitis virus G protein