RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 7–8, 2010

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' website at http://oba.od.nih.gov/oba/index.html.]

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
Minutes of Meeting[1]

December 7-8, 2010

The Recombinant DNA Advisory Committee (RAC) was convened for its 123rd meeting at 12:00 p.m. on December 7, 2010, at the Hilton Hotel and Executive Meeting Center in Rockville, Maryland. Dr. John Zaia (RAC Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 12:00 p.m. until 5:15 p.m. on December 7 and from 8:00 a.m. until 11:30 a.m. on December 8. The following individuals were present for all or part of the December 2010 RAC meeting.

Committee Members

Andrew D. Badley, Mayo Clinic and Foundation (*Day 1 only*)
Jeffrey S. Bartlett, Nationwide Children's Hospital/Ohio State University (*Day 2 only*)
Michael J. Buchmeier, University of California, Irvine
E. Antonio Chiocca, Ohio State University Medical Center
Hung Y. Fan, University of California, Irvine
Yuman Fong, Memorial Sloan-Kettering Cancer Center
Norman Fost, University of Wisconsin–Madison
Jeffrey P. Kahn, University of Minnesota
Joseph A. Kanabrocki, University of Chicago
Margaret S. Mallino, University Park, Maryland
Anna C. Mastroianni, University of Washington School of Law *(via teleconference, Day 1 only)*
David A. Ornelles, Wake Forest University School of Medicine
Susan R. Ross, University of Pennsylvania (*Day 1 only*)
Marcella Sarzotti-Kelsoe, Duke University Medical Center
Marshall Strome, St. Luke's–Roosevelt Hospital Center/New York Head & Neck Institute
James R. Yankaskas, University of North Carolina at Chapel Hill
John A. Zaia, City of Hope (RAC Chair)

Office of Biotechnology Activities (OBA)

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

Ad Hoc Speaker

K.J. Kwon-Chung, National Institute of Allergy and Infectious Diseases, NIH

Nonvoting Agency Representatives

Daniel M. Takefman, U.S. Food and Drug Administration (FDA)
Lisa A. Rooney, Office for Human Research Protections, U.S. Department of Health and Human Services (DHHS)

NIH/OD/OBA Staff Member

Chezelle L. George
Linda Gargiulo
Robert Jambou
Maureen Montgomery

[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.

Marina O'Reilly
Gene Rosenthal
Thomas Y. Shih

Attendees

There were 13 attendees at this two-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. Call to Order and Opening Remarks

Dr. Zaia, RAC Chair, called the meeting to order at 12:00 p.m. on December 7, 2010. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on November 15, 2010 (75 FR 69686). At this meeting, RAC addressed a report from the Gene Transfer Safety Assessment Board (GTSAB, a subcommittee of RAC), publicly reviewed four protocols, and discussed certification of the host vector system *Kluyveromyces lactis (K. lactis)*.

The RAC members introduced themselves by name, affiliation, and research interests.

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

II. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Fong, Kohn, Strome, Yankaskas, and Zaia

A. GTSAB Report

Dr. Yankaskas reported that 16 protocol submissions were received by the OBA in the past three months, 12 of which were not selected for public review at this RAC meeting. Of the 12 protocols not selected for public review, eight were oncology protocols, two were for monogenic diseases, one was for critical limb ischemia, and one was for an infectious disease. The vectors used in these 12 protocols were four retroviruses, four lentiviruses, two plasmids, one *Listeria monocytogenes*, and one adeno-associated virus.

Five protocols submitted Appendix M follow-up information indicating their enrollment. Of trials that had initiated enrollment in the past three months, two protocols had been reviewed by the RAC at a previous public meeting: #0401-622, Adenylyl Cyclase VI Gene Transfer for CHF, and #0906-977, Direct CNS Administration of a Replication Deficient Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human CLN2 cDNA to Children with Late Infantile Neuronal Ceroid Lipofuscinosis.

A total of 11 serious adverse events (SAEs) were reviewed by the GTSAB from six protocols, including initial and follow-up reports. After analysis of these events, the GTSAB concluded that no reports needed additional public discussion.

Dr. Yankaskas provided information about an international collaboration among GlaxoSmithKline, the Fondazione Telethon (Italy), and the San Raffaele Scientific Institute (Milan, Italy). This strategic alliance

will develop treatments to address rare genetic disorders using gene transfer carried out on stem cells *ex vivo*. The Fondazione Telethon received an upfront $15 million grant from GlaxoSmithKline and is eligible to receive further payments upon successful completion of a number of predetermined development milestones. In exchange, GlaxoSmithKline gained an exclusive license to develop and commercialize an investigational gene transfer product based on gamma retrovirus vectors for ADA severe combined immunodeficiency. In addition, GlaxoSmithKline gained rights to option lentiviral-based gene transfer products that the Institute has been working on for metachromatic leukodystrophy, Wiskott-Aldrich syndrome, beta thalassemia, mucopolysaccharidosis Type 1, globoid leukodystrophy, and chronic granulomatous disorder. Clinical trials for Wiskott-Aldrich Syndrome and metachromatic leukodystrophy were initiated in spring 2010.

Also discussed by Dr. Yankaskas was a study of stem cell gene transfer for Wiskott-Aldrich Syndrome. Published in the November 11, 2010, issue of *The New England Journal of Medicine*, the authors report the long-term (up to three years) correction of Wiskott-Aldrich Syndrome in two individuals through retroviral infection of CD34-positive hematopoietic stem cells after these cells had induced transient myelosuppression. On the same day of publication of the article, these researchers issued a press release stating that, although they had succeeded in correcting symptoms in nine of 10 research participants enrolled in their trial – one of the 10 did not receive sufficient cells – one participant who had experienced clinical benefit has developed an acute T-cell leukemia related to the experimental treatment. The vector used for that individual was an older-style retrovirus.

B. Considerations for Designing New Trials with Chimeric Antigen Receptors: RAC Safety Symposium June 15, 2010, Plus Points for RAC to Review

Dr. Corrigan-Curay presented a summary of the June 15, 2010, symposium and then proposed Points to Consider for the RAC's review and possible endorsement. Chimeric antigen receptors (CARs) are modified T-cell receptors (TCRs) that typically contain immunoglobulin single-chain variable fragments (scFV) fused as a single chain to a TCR signaling domain, with or without additional intracellular cosignaling motifs. CARs recognize surface tumor antigen by T cells in a non-HLA (human leukocyte antigen) restricted manner, which is one of their potential advantages.

The June 15, 2010, safety symposium was prompted by clinical trials using CAR T cells that showed initial promising results, in particular in a trial for neuroblastoma. However, two deaths on trials using CAR T cells, including one in which the death was assessed to be the result of an acute toxicity of the T cells, prompted a review of the trial designs. The goals of this review were enhancing safe trial design for this new and promising therapeutic approach, informing the RAC and institutional biosafety committee (IBC) review regarding future trials, and fostering exchange of information among leaders in the field.

The symposium started with the history of using CAR T cells, including the initial studies using first-generation CARs that showed limited persistence of cells. A major focus was on potential acute toxicities – the possibility that immediate binding of low levels of antigen to normal tissues could lead to a significant early toxicity through T-cell activation and cytokine release. A number of strategies were discussed that centered on how it might be possible to avoid that result in early trials by using a more conservative dose escalation, splitting dose infusions over one or more days, starting without preconditioning chemotherapy, starting with a first-generation CAR before moving to the second or third generations, and including suicide genes. Each of these strategies raised additional considerations.

The key question for discussion at the symposium was the optimum starting dose; it was acknowledged that precise recommendations for starting doses across these protocols are not possible. Factors to be considered and discussed in justifying any starting dose include the preclinical model; distribution of the antigen in normal tissue; previous experience with CAR T cells including the same CAR; whether a first, second, or third-generation CAR will be used; and whether preconditioning chemotherapy will be used. With regard to starting dose, the conclusion at the symposium was that there is not one optimum starting dose for novel targets; however, a starting dose must be clearly justified on preclinical data, distribution of the target, signaling moieties, T-cell subsets, and the use of preconditioning and cytokine support.

Conclusions from the June 15, 2010, symposium were that:

- CAR T cells have shown therapeutic benefit in initial trials; however:
  - The ability to activate T cells against tumor antigens in a major histocompatibility complex unrestricted manner not only offers a potentially potent tool for immunotherapy but also raises the risk for severe acute toxicity. Preclinical models may have limited ability to predict such toxicities.
  - Precise recommendations regarding the starting doses are not possible at this time and it is critical to justify the starting dose based on preclinical data, type of T cell, trial design, and experience to date.
  - Active research questions remain regarding optimum use of cosignaling moieties, virus-specific T cells, T-cell subsets, preconditioning, cytokine support, and suicide genes.
- Standard treatments for participants in these trials also carry risks; for example, hematopoietic stem cell transplantation may have a mortality risk of 5 to 10 percent.
- While it may not be possible to eliminate risk, the goal is to minimize risk, especially in early trials in which benefit may be less likely.

Dr. Corrigan-Curay offered the following draft Points to Consider, based on the deliberations of this safety symposium, for the RAC to discuss:

<u>General Points to Consider</u>

- A clear plan for monitoring should be in place and, at a minimum, should include provision for collection of:
  - Physiologic data
  - Cytokines, e.g., IFN-γ, IL-6, TNF-α, and others
  - Plasma and peripheral blood mononuclear cells (PBMCs) for cryopreservation
  - Routine labs from sera and urine
  - Target-organ-specific labs as indicated
- Participant screening for adequate pulmonary and cardiac function. Early reporting of SAEs and clinical outcomes are encouraged.
- Uniform dosing using a weight-based approach, e.g., cells/kg, would facilitate comparison of trials.
- Protocols that use retroviral or lentiviral vectors should monitor for the possibility of insertional mutagenesis.
- The informed consent should:
  - Discuss the risk of insertional mutagenesis.
  - Employ the terms “gene transfer” and not “gene therapy” to avoid the potential for therapeutic misconception.
- Special considerations requiring extra care:
  - Effects of CAR expression on non-T-cell populations, e.g., NK cells
  - Effects of CAR expression on specific T-cell subsets, e.g., CD8+ T cells versus all T cells or subsets of T cells; memory versus effector T cells
  - Novel vectors used to improve transduction efficiency
  - New cytokine support regimens
  - New preconditioning regimens

<u>First-Generation CARs—Points to Consider</u>

Governing Principles

- First-generation CAR T cells have shown the ability to induce inflammatory side effects.
- The survival of first-generation CAR T cells appears to be limited *in vivo* likely due to the lack of costimulatory moieties.
- Preconditioning will likely not enhance survival of first-generation CAR T cells *in vivo* but is unlikely to significantly increase the potential for toxicity from the cells.
- Cytokine support may enhance the transient proliferation and survival of transferred cells but, used in isolation, will likely not result in engraftment.

- Trials may provide a preliminary indication of safety, but to date clinical benefit has not been seen with the antigens tested.

Clinical Strategies

- Based on data from trials to date, starting doses of approximately $3x10^6$ to $1x10^7$ cells/kg have been tolerated but have had limited clinical benefit.
- A dose-limiting toxicity was seen in a European trial using a first-generation CAR against carbonic anhydrase IX for renal cell cancer after repeated infusions of T cells, at doses starting at approximately $3x10^5$ cells/kg on Day 1 to $3x10^7$ cells/kg on Days 3 and 5.
- Trials using CARs against novel targets may need to start at a lower dose.
- Preconditioning is unlikely to enhance persistence.
- Cytokine support should be considered on an individual basis relative to the goals of the study. Adequate doses of cytokines that support transient T-cell proliferation and survival without undue toxicity may be considered.

<u>Viral-Specific First-Generation CAR T cells—Points to Consider</u>

Governing Principles

- The survival of EBV-specific T cells expressing first-generation CAR has the potential to be enhanced by engagement of the endogenous TCR/costimulatory pathways on nontumor cells, e.g., infected B cells or epithelial cells.
- Preconditioning may not be needed to enhance the engraftment of EBV-specific T cells expressing first-generation CARs.
- Proliferation of EBV-specific T cells expressing first-generation CARs *in vivo* may be triggered by endogenous viral antigens at doses as low as $2x10^7$ cells/m^2 (approximately $5x10^5$ cells/kg). This dose has been associated with therapeutic effects.

Clinical Strategies

- Based on data from trials to date, moderate initial cell doses of approximately $5x10^5$ cells/kg (approximately $2x10^7$ cells/m^2) have been well tolerated.
- Initial doses for CAR T cells targeting novel antigens may need to be lower.
- Preconditioning may not be necessary to enhance persistence.
- Additional studies should be considered to assess if cytokine supplementation improves clinical outcome.

<u>Second-Generation and Third-Generation CAR T Cells – Points to Consider</u>

Governing Principles

- Second- and third-generation CAR T cells have the potential for proliferation and long-term engraftment.
- Survival and engraftment are likely enhanced by preconditioning.
- Cytokine support of transferred cells may enhance initial cell proliferation and survival, and should be investigated in more depth.
- Initial toxicity might be avoided by reducing cell dose and/or by splitting doses.

Clinical Strategies

- Dosing is based on transfer of unselected CAR T cells; selection for subsets such as CD8+ cells only may impact potential toxicity and potency.
- Data from trials to date, the majority of which have used second-generation CAR T cells, indicate initial doses ranging from approximately $5x10^5$ cells/kg up to $1x10^7$ cells/kg have been tolerated.
- An SAE possibly related to the T cells has been seen in a trial using third-generation CAR T cells at a dose of approximately $2x10^7$ cells/kg.
- An acute toxicity and death on a trial using third-generation CAR T cells occurred at a dose of approximately $2x10^8$ cells/kg.
- There is not one optimum starting dose for novel targets; starting dose must be justified by preclinical data, distribution of the target on nontumor tissue, signaling moieties, T-cell subsets and use of preconditioning, and cytokine support.

- Inclusion of cosignaling moieties as a strategy to enhance T-cell persistence and possibly efficacy is often combined with preconditioning chemotherapy to enhance engraftment. Strategies to achieve optimum engraftment while minimizing the potential for acute and longterm toxicity should continue to be studied.
- Potential benefits of cytokine support should be explored further, including:
  - Whether and when to include cytokine support
  - Which cytokine to use
  - Optimum dose

C. RAC Discussion

Dr. Fong asked whether investigators had pooled their cytokine pattern data, and whether in addition to the first dose, higher level doses should be split in later parts of the trials.

Dr. Corrigan-Curay agreed to include within the Points to Consider an elaboration on data sharing.

Dr. Buchmeier suggested avoiding use of the term “cytokine storm,” which can manifest in many different ways. He noted that it would be useful to obtain more data on the patterns of cytokines to determine commonalities, which might hint at potential therapy.

D. Committee Motion 1

Dr. Fong moved and Dr. Buchmeier seconded that the RAC support Dr. Corrigan-Curay’s presentation and Points to Consider as recommended. Dr. Zaia clarified that this vote would support the concepts as expressed at this meeting, and that a document would be finalized at a later date. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Discussion of Human Gene Transfer Protocol #1010-1073 Entitled: An Open Label, Non-Randomized, Single Dose, Multi-Center Phase II/III Study of the Safety and Efficacy of Lenti-D Modified Autologous Stem Cells (Lenti-D Drug Product) for the Treatment of Subjects with Childhood Cerebral Adrenoleukodystrophy (CCALD)

Principal Investigator:	David A. Williams, M.D., Children’s Hospital Boston
Additional Presenters:	Patrick Aubourg, M.D., INSERM and University Paris-Descartes, France; Florian Eichler, M.D., Massachusetts General Hospital
Sponsor:	Philip Reilly, M.D., bluebird bio, Inc.
RAC Reviewers:	Drs. Fost, Ross, and Zaia

Dr. Kohn recused himself from consideration of this protocol due to a conflict of interest.

A. Protocol Summary

Bluebird bio is developing Lenti-D for the treatment of Childhood Cerebral Adrenoleukodystrophy (CCALD), a rare, life-threatening, genetic disease for which safe treatment options are lacking. CCALD occurs with a yearly incidence of approximately 1/40,000 live male births and is typically diagnosed in boys between the ages of 3 and 15 years. Initial symptoms include a deterioration of cognitive and motor function- manifestations of underlying cerebral demyelination and inflammation detectable by magnetic resonance imaging (MRI) brain scan. If left untreated, as neurons in the brain continue to lose their insulating sheath (myelin), which is essential for the proper function of nerves, patients lose their ability to function independently, enter a vegetative state, and typically die approximately five years after the original diagnosis.

CCALD is an X-linked disease caused by loss of function mutations in the ABCD-1 gene, which encodes the ALD protein (ALDP) - a peroxisomal transporter involved in the breakdown of very long chain fatty acids (VLCFA). While it remains unclear how elevated VLCFA levels in CCALD

patients lead to demyelination, it is believed that an inflammatory response is involved as an initial trigger. A reduction of VLCFA levels through the use of special diets (such as Lorenzo's Oil) may slow time of onset of the disease, but has not proven sufficient to halt the progression of the disease once established.

To date, allogeneic hematopoietic stem cell transplant (HSCT) is the only intervention that has been shown to arrest CCALD progression. While the mechanism of therapeutic efficacy remains to be fully understood, it is believed that arresting the disease over a 12-18 month period results from donor derived macrophages migrating across the blood-brain-barrier and differentiating into ALDP producing microglia. It has been found that patients with a Loes score(a 34 point demyelination MRI score routinely used in CCALD) of 9 or lower experience disease stabilization following HSCT. Yet even in these patients, transplant associated adverse events present a significant risk of morbidity and mortality. Whether using HSCs from bone marrow aspirates, mobilized CD34+ cells, or umbilical cord blood, severe graft versus host disease(GVHD) is the lead cause of mortality after transplantation. It is estimated that even at the best transplant centers approximately 15% of patients suffer transplant related mortality, and that an even greater number (~30%) experience GVHD.

As a safer alternative to allogeneic HSCT, bluebird bio is developing Lenti-D – a lentivirus based autologous cell therapy to restore functional ALDP production in a patient's own hematopoietic stem cells, thereby eliminating the risk of GVHD. The promise of lentiviral gene therapy in this indication has been demonstrated in a French Phase 1/2 study in which three subjects were transduced ex vivo with a lentiviral vector encoding the ABCD-1 gene under control of the MND promoter. In 2-4 years of posttreatment follow-up, all three subjects have experienced disease stabilization. In addition, no serious adverse events have been reported and the subjects remain polyclonal for ABCD-1 insertion, with no indication of clonal dominance. Based in part on these results, and on additional supporting pre-clinical data, bluebird bio aims to initiate a 12 subject registration in 2011.

B. Written Reviews by RAC Members

Seven RAC members voted for in-depth review and public discussion of the protocol. Key issues included that this is the first protocol for this disease and vector to propose enrollment in the United States, although encouraging results were seen in the initial three research participants in a French trial. As the proposed population is considered vulnerable and an established alternative treatment exists, the selection of the population and design of this Phase II/III study were deemed to deserve in-depth review. In addition, further discussion was considered warranted regarding the risk/benefit of using the self-inactivating lentiviral vector for disease in this population.

Three RAC members provided written reviews of this proposed Phase II/III trial.

Dr. Fost stated that this protocol is well constructed and the informed consent document (ICD) is clear and candid, but that the proposed intervention carries substantial risks that include failure of engraftment and later hematopoietic malignancy. The investigators propose primary endpoints of a less-rapid rate of decline, measured during any consecutive 6-month period by a change in Loes score, as well as a decline of less than 15 points in performance IQ during any consecutive 6-month period. Dr. Fost requested to see control data for the rate of change in those measures in undosed children and/or children who received stem-cell transplants.

Dr. Ross requested clarification of several parts of the protocol. While the protocol discusses three research participants enrolled in the French ALD trial, the 2010 *Science* publication describes only two of those participants; she asked the investigators to provide information about the third participant. Dr. Ross queried as to the exact time of follow-up and the rationale for this timing, and whether enrollment in the separate protocol for longer follow-up would be required or optional. She asked the investigators to clarify the rationale for staggered enrollment of the first two participants and whether the 12 enrollees for this trial would be from the United States or would also come from Europe; she also wondered about the basis for halting the trial after engraftment of the first participant. Dr. Ross asked the investigators to

elaborate on the basis for requesting withdrawal of a participant and whether participants who are able to undergo matched sibling HSCT would be eligible for this trial, given that HSCT has a high success rate.

Dr. Zaia asked the investigators to discuss the mobilization and collection procedures that will be used to collect sufficient peripheral blood stem cells (PBSCs) in this pediatric population, focusing on the likelihood that one or two days of collection will be sufficient. He requested that the investigators justify the definition of performance IQ stabilization as a decline in performance of less than 15 points in a 6-month period, and he asked as to whether this trial would include potential surrogate markers of performance improvement that could be validated during this study for future use as primary endpoints. Because the long-term follow-up period is 15 years, Dr. Zaia inquired as to the existence of a contingency plan in case the investigators or the sponsor are not available for this length of time. With regard to the ICD, Dr. Zaia noted that it is generally well written, with a few items needing attention. Because it will be difficult in the consenting environment to maintain uncertainty when explaining the relative merits of standard of care vs. the results to date for the three boys in the French trial, he suggested explaining the facts in more detail and with less interpretation, to include the differences between the French method and the method of this trial and presentation of the facts that indicate an interruption of disease progress by the gene transfer in the French study. Dr. Zaia also suggested that it be made clear whether the allogeneic treatment option ceases when the research procedure is chosen and that the method by which a research participant can withdraw from the study be provided.

C. RAC Discussion

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

- Dr. Fost suggested that the investigators add language to the ICD that discusses the risk that the life of a child-participant could be prolonged but function decline irreversibly before the effect of the gene transfer.

- Dr. Kahn asked the investigators to explain how they believe they meet the regulatory requirement that this proposed trial offers at least as favorable a risk/benefit balance as the available alternative approaches. He stated the equipoise question – whether the investigators can, in good conscience, offer parents this protocol versus another alternative and conclude that one is not better than the other. If the investigators can answer that question affirmatively, then they can go forward with this protocol; if they cannot answer affirmatively, Dr. Kahn stated that a basic ethics problem emerges.

- Dr. Fost suggested that this trial would be improved by the addition of consent monitoring and an independent consent advocate.

- Dr. Zaia asked whether reversal of the demyelination occurs with cellular-based therapy.

- Given that the transplanted gene-modified cells repopulate the glial cells in the brain but may not stay there permanently, Dr. Yankaskas asked the investigators whether they would consider a follow-up redosing with the genetically modified cells beyond the two and a half years of follow-up currently proposed.

D. Investigator Response

1. Written Responses to RAC Reviews

Because no multicenter, large cohort of patient outcomes in this disease is currently available, bluebird bio is conducting a retrospective data collection study in CCALD across three clinical sites in the United States and one in France in order to better understand the natural history of the disease. The study will look at patients who received allogeneic stem cell transplants as well as patients who did not receive a transplant. This study is expected to strengthen understanding of the disease, and to refine the

investigators' choice of clinical endpoints and study design. These data will be filed in support of the IND application.

With regard to information about the third and fourth participants in the French trial, Participant 3 was transplanted in June 2008, following the same transduction and transplant protocol as used for the first two participants. Upon transduction, Participant 3's CD34 cells harbored the Lenti-D provirus at a vector copy number of 0.63, and long-term follow-up until month 28 has demonstrated stabilization of 0.11 vector copies in CD34 cells. This individual experienced no SAEs. Detailed insertion site analysis has been performed and the reconstituting hematopoietic cells have remained fully polyclonal, with no evidence of clonal skewing or clonal dominance. In terms of therapeutic efficacy, while measures of performance and verbal IQ have not yet stabilized, the participant's Loes score has remained stable for the last 8 months of follow-up and the investigators continue to monitor this individual. In September 2010, a fourth research participant was dosed and a vector copy number of 0.62 was achieved in his CD34 cells before transplant. In the 45 days of follow-up since transplant, no SAEs have been reported.

The length of time on study under this proposed protocol (ALD-102) is 30 months. There will be a separate long-term follow-up protocol, ALD-103, that will follow the study participants from Month 30 to 15 years posttransplant. When the individual consents to be enrolled in the first trial, the investigators will inform him that, upon completion, he will be asked to participate in the ALD-103 trial in order to provide long-term follow-up of the experimental treatment. Participation is always optional, and a study participant has the right to withdraw his participation at any time.

While the investigators currently lack access to CD34 cells from ALD patients, they are in the process of acquiring this material and will carry out additional experiments demonstrating the full range of ALDP expression once the cells are obtained.

This trial will enroll 12 participants from U.S. and European sites, as described in Appendix M. Language will be clarified to address this point.

The investigators explained the rationale for the staggered enrollment, which is to mitigate the safety risk of Lenti-D transduction on HSC engraftment. The Lenti-D vector has not yet been used in humans, and staggered enrollment will be employed as an added safety measure to allow for a more controlled start of the study and to minimize the risk of any unforeseen issues related to engraftment. Failure of two participants to engraft applies to any two participants in the study. Integration site analysis will be performed according to timelines in the clinical protocol; however, the investigators do not expect integration analysis to yield meaningful safety data during the period of engraftment of the first two participants.

Up to the point of myeloablation, if in consultation with the investigator, a participant is deemed to be non-compliant with the study requirements, he will be withdrawn from the study.

Even though HSCT seems to have a high success rate in CCALD patients, individuals who can undergo matched sibling HSCT will still be eligible to participate in this trial. Because of the small but significant risk of morbidity and mortality even in an allogeneic transplant between HLA-identical siblings, the investigators believe that parents should have the right (after consultation with their physician) to consider enrolling their son with CCALD in this clinical trial.

The investigators estimated that two days of PBSC collection would be sufficient, but stated that it would be reasonable and safe to continue collection for a longer period. They based their response on information from 57 patients who had pre-HSCT apheresis in 2009 and 2010 at Children's Hospital Boston. The three of these 57 patients who did not achieve their apheresis goal had been heavily pretreated with chemotherapy. The average number of days to achieve the apheresis goal was 1.7 days with a range of 1 to 7 days; greater than 80 percent of these patients attained their apheresis goal in two days and 94 percent successfully apheresed in three days or fewer. There is a paucity of published literature validating endpoints to define successful treatment of CCALD with allogeneic HCT; the available

literature mainly provides survival data, rather than details on functional status. It is possible that the investigators' planned retrospective data collection study will identify new clinically relevant markers.

Regarding providing follow-up for 15 years, the investigators explained that patients with this complex medical condition will be seen regularly throughout their life, which is considered standard of care. In addition, Children's Hospital Boston has taken out additional liability coverage for Phase I trials to cover research-related injury and bluebird bio will have the appropriate insurance in place prior to the first participant being dosed. To comply with the FDA guidance on long-term follow-up for gene transfer studies, the investigators plan to develop an NIH grant application that will encompass safety, efficacy, and insertion site monitoring during the follow-up period. (Currently no conforming NIH mechanism exists to provide funding for follow-up periods longer than five years.) Should bluebird bio be merged into or acquired by another entity, its obligation to the participants in this study will be assumed by the new entity. Should bluebird bio cease to exist due to bankruptcy, the sponsor would move to protect sufficient assets to guarantee that the required follow-up is performed. Because these follow-up studies will be conducted according to an agreed-upon protocol, a competent pediatric neurologist and an expert in insertional mutagenesis could do this work, regardless of the location of her/his home institution.

The investigators agreed to edit the informed consent document to restore equipoise; the ICD will explain the facts about the trial with the French participants, the ICD will emphasize uncertainty as to both short-term and long-term risks and benefits, and the consent process will neutrally describe the post dosing disease trajectory of the dosed boys. To date, no SAEs have been reported in the French trial. Two lines of evidence indicate an interruption of disease progression in the French trial: stabilization of the MRI scores and stabilization of the performance IQ scores.

The investigators explained that it is standard practice in oncology patients to wait as long as six months between autologous and allogeneic transplants, to reduce the risk of procedure-related organ toxicity. In the case of CCALD, if in the opinion of the research participant's neurologist and transplant physician the risk of disease progression outweighs the risk of allogeneic transplant following autologous transplant, then allogeneic transplant could occur sooner.

2. Responses to RAC Discussion Questions

Dr. Williams explained that the data from the French study form the basis of the argument that this proposed trial offers at least as favorable a risk/benefit balance as the available alternative treatments. The participants in that trial have had outcomes that are equivalent to transplant outcomes and have no risk of GVHD. GVHD is difficult to treat, can lead to morbidity and mortality, and can have a severe effect on disease progression.

With regard to the question of equipoise, Dr. Williams stated that, in the X-linked severe combined immunodeficiency trial, his institution employs an unbiased faculty member who meets with the family after the initial consenting process to make sure there is no bias in presenting the alternative to trial participation. That faculty member must assure the institutional review board (IRB) that the family truly understands the alternative therapies and the risk of participating in the current clinical trial. He suggested that such an arrangement might be appropriate for this proposed trial.

Dr. Eichler explained that he has not seen reversal of the demyelination with cellular-based therapy. The best outcome that can be expected is stabilization and no progression of demyelination.

With regard to the possibility of redosing participants after the official follow-up period, Dr. Williams explained that successful engraftment of a large number of cells with concomitant high chimerism rates means that the disease is stabilized for the long term. In this type of experimental therapy that inserts a gene that could be silenced, it would be possible to redose even though redosing is not currently written into the protocol.

Dr. Williams explained that the natural history of this disease has two peaks, which are biologically different diseases. This trial proposes to address cerebral ALD and not the adult (spinal cord) form of the disease.

E. Public Comment

Ms. Rooney offered several comments about the informed consent document:

- All references to "treatment" should be reworded to avoid therapeutic misconception.
- It would be helpful for the parents to know how long and when their children might be hospitalized as a result of their participation in this trial.
- The possibility that participation in this gene transfer trial might preclude participation in other gene transfer trials in the future should be specified.
- An assent form may be needed for this trial.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

<u>Ethical, Social, and Legal Issues</u>

- The protocol proposes enrollment of participants who would also be eligible for HLA-matched allogeneic stem cell transplant. Inclusion of such participants is based on assessment that there is a reasonable research question as to whether gene transfer is as effective as matched allogeneic stem-cell transplant, the only effective treatment currently available. That assessment is based upon the therapeutic benefit observed in three participants in a previous ALD gene transfer trial that used a similar vector and transgene. This reasoning should be communicated in the consent process, along with information about the risks and benefits of allogeneic stem-cell transplantation, in order to ensure that parents who are considering enrolling their children in this protocol understand both options and the data supporting each approach. Given the complexity of this consent process, it would be useful to establish a procedure to monitor the adequacy of the consent process and to consider whether the consent process should be conducted by individuals other than the principal investigators or co-investigators who are directly involved with the research, or should at least involve clinicians who are not investigators on this protocol.

- Based on the time needed for the transduced cells to engraft, it is expected to take 12 months or more to observe MRI and performance IQ stabilization in research participants. Because CCLAD is a rapidly progressive disease and the gene transfer is expected to halt but not reverse its progression, there could be a significant decline in neurological function between the time the gene-modified cells are administered and any therapeutic benefit. As a result, the gene transfer could prolong life but not prevent significant neurological decline. While this may also be the case for allogeneic stem cell transplantation, the informed consent process should discuss this possible outcome.

- The informed consent document could be improved by the following:

    - Inclusion of discussion as to whether enrollment in this trial could potentially limit the ability of the participants to pursue alternative treatments, such as allogeneic transplantation or enrollment in other gene transfer trials
    - More specific information regarding the procedures required during the trial, (e.g., length of hospitalization) and possibly a separate informed consent document for certain anticipated procedures such as bone marrow aspiration
    - Removal of any reference to the intervention as "treatment"

G. Committee Motion 2

Dr. Zaia orally summarized the RAC recommendations to include a variety of ethical/social/legal concerns that will be included in the letter to the investigators expressing the comments and concerns of the RAC. It was moved by Dr. Yankaskas and seconded by Dr. Bartlett that the RAC approve these summarized recommendations. The vote was 14 in favor, 0 opposed, 0 abstentions, and 1 recusal (Dr. Kohn).

IV. Discussion of Human Gene Transfer Protocol #1010-1074 Entitled: Phase I Clinical Intramuscular Gene Therapy of rAAV.FS344 Trial to Patients with Becker Muscular Dystrophy and Sporadic Inclusion Body Myositis

Principal Investigator:	Jerry R. Mendell, M.D., Nationwide Children's Hospital
Additional Presenters:	K. Reed Clark, Ph.D., Nationwide Children's Hospital; Kevin Flanigan, M.D., Nationwide Children's Hospital; Brian M. Kaspar, Ph.D., Nationwide Children's Hospital; Xiomara Rosales, M.D., Nationwide Children's Hospital
RAC Reviewers:	Dr. Fong, Ms. Mastroianni, and Dr. Ornelles

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

A. Protocol Summary

The investigators propose to perform a gene transfer clinical trial in Becker muscular dystrophy (BMD) and sporadic inclusion body myositis (sIBM) patients. Presently there is no treatment that can reverse BMD or sIBM; only supportive care is currently possible.

Both of these conditions have the common feature of loss of ability to walk because of weakness of the thigh muscles. The investigators propose a gene transfer trial to deliver to muscle a gene called follistatin (FS344) that can build muscle size and strength. If successful, it may be possible to increase the size of the thigh muscle and potentially prolong a patient's ability to walk. The gene will be carried into the muscle by an adeno-associated virus (AAV) that does not cause any human disease.

In this study, research participants with BMD or sIBM will have the follistatin gene injected directly into thigh muscle on both legs. The muscle will undergo biopsy 180 days following the gene delivery to determine if the muscle fibers are bigger. Between the time of the gene transfer and the muscle biopsy, participants will be monitored carefully for any side effects of the experimental treatment; monitoring will include an MRI of the thigh muscle before dosing and at day 180 following dosing.

Blood and urine tests as well as physical examination will be conducted on the research participants during the screening visit and on days 0, 1, 2, 7, 14, 30, 60, 90, and 180 to make sure that there are no side effects from the gene injections. Sutures will be removed two weeks post biopsy. Additional blood samples will be collected at nine, 12, 18, and 24 months. Participants in this trial will be seen at the ends of year one and year two for a physical examination, assessment of muscle strength, and appropriate blood tests.

B. Written Reviews by RAC Members

Four RAC members voted for in-depth review and public discussion of the protocol. Key issues included the use of a novel transgene to treat these diseases.

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

Dr. Fong offered several suggestions and asked several questions with the goal of improving the proposed study.

- Are the risks and benefits of participation in this study the same with regard to patients with BMD and sIBM? Do the timeline and predictability of deterioration of these two diseases provide for future Phase III trials?
- The research participants for this study should have a well-defined level of disability; for example, would wheelchair-bound individuals be expected to attain more benefit compared to less-disabled individuals?
- At follow-up at 9, 12, 18, and 24 months, thigh girth could be used to judge persistence of viral gene expression or muscle hypertrophy. It is possible that persistence of gene expression could help define how often a research participant might need to be dosed with virus.
- In the primate studies and other preclinical studies, how long did follistatin expression and secretion persist?
- Can serum levels of follistatin be used to monitor persistence of gene expression? Have injections or infusions of follistatin protein been tried for purposes of monitoring gene expression?
- What data supports the requirement that research participants practice a reliable method of contraception during the two years of the study?
- Might it be possible to inject one thigh and use the other side as a control, with independent quadriceps tests?
- If follistatin is a human protein, why would research participants form an immune response to it?

Ms. Mastroianni commended the investigators for their attention to detail in the ICD. Since BMD and sIBM are not life-threatening conditions and because this is a Phase 1 trial, she noted that clarity and accessibility of information presented during the informed consent process are especially important. She asked whether the investigators plan for long-term follow-up should pregnancy occur after the injections, and noted that the ICD does not mention the possibility of longer-term follow-up, if required pursuant to FDA guidance. In three sections of the ICD and in one section of the protocol, Ms. Mastroianni requested that the investigators ensure clarity and consistency of the language regarding the timing of sharing of information with participants. She also noted that the protocol and Appendix M conflict regarding the permissibility of continued aspirin therapy before and during drug administration.

Dr. Ornelles asked whether any level of pre-existing immunity to AAV would constitute cause for a potential research participant to be excluded from this trial. He asked the investigators to specify the criteria for a clinically meaningful result, since such a result in one cohort would preclude an increase in dose for the next cohort; he was particularly concerned that a valuable dose escalation might not happen because of a statistically significant but biologically trivial increase in muscle strength. Dr. Ornelles expressed concern about the unknown effect of expressing an agent with the potential to cause significant muscular hypertrophy. In the animal studies in mice and monkeys reported by the investigators, expression of the follistatin gene variant led to measurable increases in muscle mass, fiber size, and fiber number. If the efficacy seen in mice and monkeys is even more pronounced in humans (which is possible, given that the gene product, virus, and promoter were all human-derived), the level of follistatin and extent of muscular hypertrophy could be problematic. Dr. Ornelles stated his concern about possible off-target effects of the soluble follistatin in other muscles, including nonskeletal muscles such as those in the heart and uterus; he requested that the investigators give more attention to the potential adverse effects that might occur due to high systemic follistatin levels. He suggested that a database or similar resource of normal muscle morphometry could prove useful when compared with the data derived from this study. On balance, Dr. Ornelles stated that evidence for the potential benefits warrants proceeding with this study, with appropriate concerns for off-target effects of follistatin.

C. RAC Discussion

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

- Dr. Zaia asked for clarification of the age of eligibility for this protocol.
- Dr. Fost expressed concern about the presence in the ICD of a long list of entities that would have access to identifiable private health information from participants in this clinical trial.

- Dr. Strome asked the investigators to explain why they are using the 6-minute walk test (6MWT) as an outcome measure but not as an inclusion criterion.

D. Investigator Response

1. Written Responses to RAC Reviews

The timeline for sIBM from onset to wheelchair dependency is about 8 to 10 years. Loss of ambulation is more unpredictable for BMD since it is defined by the quantity and quality of dystrophin. Although great variation occurs, commonly BMD patients walk until the fourth or fifth decade. In both sIBM and BMD patients, the criteria for admission to this gene transfer trial will be quadriceps' muscle weakness. The investigators' intent is to prolong ambulation by strengthening the thigh muscle, which will improve quality of life.

Quadriceps muscle weakness is the requirement for enrolling research participants. The investigators explained that it would be a risk to use wheelchair dependency as an inclusion criterion, considering that this degree of disability would include individuals with virtually no quadriceps muscle remaining and thus would predict a diminished or no response following gene transfer.

The efficacy of gene expression will be tested directly in two ways: 6MWT and muscle fiber size on muscle biopsy with pre and post gene transfer comparison. Muscle girth will be added to the protocol, as suggested by one RAC reviewer, but the investigators consider this measure to be relatively insensitive because small increases in muscle size might not be detected but could improve function.

In the mouse, the investigators found persistence of gene expression for as long as two years, as measured by increase in muscle fiber size and increase in grip strength. In the nonhuman primate, the studies were stopped at 15 months and increase in muscle fiber size was found at this time point. Follistatin secretion within the muscle tissue was also found at necropsy (15 months) in the monkey.

The investigators have attempted to follow follistatin serum levels over time but have found the assay to be variable. Therefore, they have used follistatin measurements in the muscle as a more reliable indicator of gene expression.

It is impractical to deliver the follistatin protein intravenously, because the half-life is 4.0 minutes and the terminal half-life is 130.8 minutes. Most of the accumulation following intravenous delivery is in the liver, and even there after two hours only nine percent follistatin is detectable.

The investigators plan to perform a semen test in male participants three months after gene transfer. Testing will continue every seven days until two consecutive negative samples are obtained, at which time male participants will no longer need to maintain contraception; the investigators agreed to modify the protocol accordingly. For the women entering the trial with sIBM, there will be little cause for concern because the disease usually affects postmenopausal women.

In response to the suggestion that they inject one thigh and use the other side as control, the investigators stated that they had originally proposed a protocol following this paradigm. However, the FDA did not want them to move forward with this protocol because of concern about producing clinical asymmetry for the research participant that potentially would be burdensome.

While follistatin-targeted immune responses have not been observed in preclinical animal studies to date, it is a theoretical possibility and has been observed with a self protein following AAV muscle administration in nonhuman primates. Therefore, the investigators agreed to monitor immune responses to the transgene to determine if CD4, CD8, or B-cell reactivity is present following follistatin 344 gene expression.

The investigators would continue to follow a participant who becomes pregnant following gene delivery, although such an event is unlikely because of the expected age of the sIBM participants. A statement has been included in the ICD to address this issue.

Based on current FDA guidelines, the investigators believe this trial will not require long-term follow-up observations for delayed AEs. Current FDA guidelines call for two-year follow-up for AAV gene transfer trials that are unlikely to result in delayed AEs. All preclinical data and experience in two previous FDA-approved AAV gene transfer trials indicate that two-year followup will be sufficient.

The investigators agreed to clarify that patients on aspirin or other drugs that could affect coagulation should continue their medication as indicated.

Accumulating evidence in gene transfer studies suggests that research participants with preexisting immunity to AAV poorly transfect muscle upon gene transfer; however, it has been difficult to establish the preferred level of neutralizing antibody that should preclude trial participation. The investigators propose to use the neutralizing antibody titer that precluded gene expression in their recently published alpha-sarcoglycan gene transfer trial. Based on those findings, they will exclude individuals with AAV1 titers of 1:1600 dilution and greater.

The investigators will state clearly that a 15 percent increase in distance covered in the 6MWT will define clinically meaningful improvement. If two of three participants at any dose level improve to this degree, they will hold the dose at this level and administer that same dose to the next cohort.

In their preclinical preparation for this proposed trial, the investigators conducted full batteries of chemistries, an endocrine workup, and full necropsies on every nonhuman primate studied. They found no evidence of histological abnormalities in the cardiac muscle of the nonhuman primates. Morphometric analysis showed no differences in cardiomyocyte diameter between AAV, follistatin and controls. The chemistry profile in the monkeys at five and 15 months post gene delivery showed normal creatine kinase readings, suggesting no cardiac damage.

With regard to concerns about uterus hypertrophy, the investigators have data from preclinical autopsies and 6-week and 12-week toxicology studies from the cynomolgus macaques that showed normal size uterus and additional data that show normal menstrual cycles.

The investigators have amended their protocol to conduct a muscle biopsy on one leg prior to dosing and to do the post gene transfer biopsy on the opposite leg at day 180. This procedure affords the greatest likelihood of seeing a shift in fiber diameter toward larger fibers.

2. Responses to RAC Discussion Questions

Dr. Mendell explained that the investigators have collected a great deal of data that shows a correlation between quadriceps weakness and the 6MWT. To avoid the possibility of a negative study, the investigators want enough quadriceps muscle preserved in order to show a clinical effect. If a clinical effect can be achieved, a subsequent trial would explore whether function can be improved, using either vascular delivery or more severely disabled research participants.

The investigators clarified that patients must be at least 18 years old to participate in this clinical trial.

Dr. Kaspar explained that evaluating follistatin expression in the liver is justified; however, based on expected levels and the delivery of AAV1, the investigators are not concerned about its presence.

With regard to which entities would be able to receive identifiable private health information, Dr. Mendell agreed to re-examine the list of such entities in the ICD and to exclude as many as possible, in consultation with their IRB.

Dr. Mendell explained the investigators' goal in looking at muscle strength as an inclusion criterion, which was to demonstrate that muscle weakness or strength is not a measure of functional outcome. The investigators have examined the relationship between muscle strength and the 6MWT. While the primary clinical entry to the study will be muscle weakness of the quadriceps, the outcome after gene transfer will be the 6MWT, with muscle strength as a secondary outcome. By adding muscle strength as a secondary outcome, the investigators hope to add to the realization that muscle strength has a role in clinical outcome for muscle disease.

Regarding the rationale for dosing two legs instead of just one, the investigators explained that if only one leg were to be dosed in this trial and clinical efficacy occurs in that one leg, the research participant would have asymmetry of muscle strength.

The investigators agreed to add to the inclusion criteria the range of percent of normal of the 6MWT result that would allow a patient to be included in this clinical trial.

E. Public Comment

Mr. Terry Anderson stated that his wife was diagnosed with sIBM within the past 3 years. He described her experiences from the initial symptoms to her current limitations. They attended the national patient conference on myositis in St. Louis last September. He explained that "We went to the conference thinking that maybe we would meet someone with good news about a cure or a treatment for SIBM. This was not to be. We talked with numerous patients and caregivers alike and the stories are all similar: everyone was hopeful for a cure but mostly they were looking for accommodation tips because a cure seems out of reach. The best news we heard at the conference was the news of this study and we came away with some hope. We are excited about the potential of this treatment and we hope and pray that it goes forward and meets with success. I would love to see Bitsy pain-free and back on the bike again."

Ms. Rooney noted that the process of declining autopsy, as stated in the ICD, needs to be clarified. In addition, she requested that the investigators remove language at the signature line of the ICD that states, "[b]y signing this consent form, I certify that all health information I have given is true and correct to the best of my knowledge." She explained that that statement does not constitute the purpose of signing an informed consent document.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

<u>Clinical and Trial Design Issues</u>

- This study currently proposes to enroll a total of 18 participants (nine with Becker muscular dystrophy and nine with sIBM) into three cohorts. The dose for the first cohort is $1x10^{11}$ vg (vector genomes)/kg into each quadriceps muscle; proposed doses for each of the next two cohorts will be raised by a half-log. As currently proposed, if only a modest effect is observed at the highest dose ($6x10^{11}$ vg/kg), the trial does not allow for the possibility of enrolling participants into a higher dose cohort. The investigators may wish to consider adding an additional dose escalation cohort beyond the current proposed highest dose.

- One of the inclusion criteria is that participants must be ambulatory and have "weakness" in the quadriceps muscle. Since these diseases are slow to progress, there is a range of weakness in patients. More specific criteria for quantifying quadriceps' weakness should be included, perhaps using the 6MWT or another objective measure.

- Currently, any Grade II AE, as defined in the Common Terminology Criteria for Adverse Events, is considered to be a dose limiting toxicity (DLT). However, given the seriousness of these diseases and the fact that certain Grade II events may not be clinically significant, consideration should be given to tailoring the definition of DLT to certain clinically important Grade II events or even to consider whether Grade III events should primarily be used to define a DLT.

- Follistatin expression could potentially affect cardiac muscle. It is reassuring that, in the nonhuman primate studies conducted, no histological abnormalities were seen in the cardiac muscle. However, given this concern, the protocol should include ongoing monitoring of cardiac function using echocardiograms.

- Published studies link follistatin to cancer, in particular hepatocellular carcinoma. While this is not definitive data and much of the literature linking follistatin to malignancy relates to a different form (the nonsoluble form) of follistatin, the investigators should consider whether the current monitoring plan is adequate to detect an increase in the appearance of cancer or whether additional studies are warranted.

Ethical, Social, and Legal Issues

- If the protocol is revised to more specifically monitor for malignancy, the informed consent should be revised to include a discussion and rationale for this monitoring. Likewise, the rationale for cardiac monitoring should be discussed.

- The informed consent document could be improved by the following revisions:

    - Remove all references to a "legally authorized representative," since only competent adults are eligible to participate in this study.
    - Provide more detail on the "experimental" procedures that will be performed on the blood collected during the follow-up visits and explain why these studies are considered experimental.
    - Replace the term "gene therapy" with "gene transfer" to help avoid therapeutic misconception.
    - Clarify more specifically the type of data that will and will not be submitted to outside regulatory bodies. Some types of data, such as the date of dosing or medical history information, might be included in SAE reports. However, data that is not essential – for example the participant's name, social security number, or medical record number – generally should not be necessary to disclose as part of ongoing oversight by outside bodies, including the OBA.

- Currently, the ICD includes the following statement: "[b]y signing this consent form, I certify that all health information I have given is true and correct to the best of my knowledge." This statement seems out of place and not consistent with the purpose of the informed consent document, which is to educate the participant about the proposed research. If enrollment in the trial is dependent upon submission of medical information by the participant, a separate document asking the participant to attest to the veracity of the information submitted would be preferable.

G. Committee Motion 3

Dr. Zaia orally summarized the RAC recommendation to include several clinical and ethical/social/legal concerns that will be included in the letter to the investigators expressing the comments and concerns of the RAC. It was moved by Dr. Fong and seconded that the RAC approve these summarized recommendations. The vote was 16 in favor, 0 opposed, 0 abstentions, and 2 recusals (Drs. Bartlett and Chiocca).

V. Certification of Host Vector System: *K. lactis*

Presenter: Dr. Kanabrocki
Ad hoc Presenter: K.J. Kwon-Chung, Ph.D., National Institute of Allergy and Infectious Diseases, NIH

A. Presentation by Dr. Kanabrocki

The Office of Biotechnology Activities received a request from the IBC of New England BioLabs to consider two strains of *K. lactis* and their associated plasmids as a host vector 1 (HV1) system, and to exempt certain research with this host vector system from the *NIH Guidelines*. According to the *NIH Guidelines*, a host-vector system is a combination of vector and host so as to provide a level of biological containment to minimize: 1) survival of the vector in its host outside of the laboratory, and 2) transmission of the vector from the host to other non-laboratory hosts. Most of the plasmid vectors included in this request are derived from a plasmid called PGBN1, an *E. coli – K. lactis* shuttle plasmid designed to integrate into the *K. lactis* chromosome at the LAC4 promoter locus. In reviewing this request, the Biosafety Working Group of the RAC and *ad hoc* experts considered the information provided by New England BioLabs as well as background information, including historical perspectives of how the RAC has dealt with host vector systems in the past.

Information to be considered when petitioning certification of an HV1 system includes:

- The strain's natural habitat and growth requirements
- Physiological properties including those related to reproduction, survival, and mechanisms by which genetic information is exchanged
- The range of organisms with which that organism normally exchanges genetic information and the type of information exchanged
- Relevant information about its pathogenicity or toxicity
- A description of the history of the strain and vectors to be used, including data on any mutations that could render the organism less able to survive or transmit genetic information
- A general description of the range of experiments contemplated, with an emphasis on the need for developing the host vector system

In terms of its natural habitat and growth, *K. lactis* is a natural, indispensable component of cultured dairy processes for producing yogurt, cheese, and buttermilk. It possesses a highly expressed βgalactosidase that degrades lactose to galactose, and glucose monosaccharides. Fermentation results in the production of acetic acid and ethanol, while growth under aerobic conditions produces no ethanol. Optimum growth for this organism is 30 °C and it replicates poorly at temperatures above 34 °C, thereby limiting its survival within humans and most warm-blooded animals.

In terms of its pathogenicity and toxicity, *K. lactis* is isolated naturally from dairy products and has been used extensively in the food industry to express heterologous proteins such as recombinant bovine chymosin (a rennet enzyme) and lactase, both of which have been granted GRAS ["generally regarded as safe"] status by the FDA. An oral form of purified native lactase isolated from *K. lactis* has been used to treat lactose intolerance, and a dried, inactivated *K. lactis* powder has been used as a human dietary supplement. No known acute pathogenicity or toxicity have been described for this organism.

Under the current *NIH Guidelines*, research with these strains and associated plasmids may be conducted at biosafety level (BL) 1 but must be registered with the IBC. Large-scale growth (greater than 10 liters) would be conducted under BL1 large-scale conditions, as described in Appendix K of the *NIH Guidelines*.

Dr. Kanabrocki explained that the RAC needs to consider two questions related to this request:

1. Do the non-recombinant, lab-adapted strains of *K. lactis* and associated plasmids satisfy criteria for HV1 certification?

2. If *K. lactis* is eligible for certification, should certain research with this newly certified HV1 system be exempt from the requirements of the *NIH Guidelines*?

The language proposed to be added to Appendix C of the *NIH Guidelines* is as follows:

> "Experiments involving *Kluyveromyces lactis* host vector systems, with the exception of experiments listed in Appendix *(new)*-A, are exempt from the *NIH Guidelines* provided laboratory-adapted strains are used. For these exempt experiments, BL1 physical containment is recommended. For large-scale fermentation experiments, the appropriate physical containment conditions need be no greater than those for host organisms unmodified by recombinant DNA techniques. The IBC may specify higher containment if deemed necessary."

B. RAC Discussion

Dr. Kwon-Chung explained that, although some cases of fungemia are caused by *Saccharomyces cerevisiae*, no such problem is associated with *K. lactis*. If certain research with *Saccharomyces* (a certified HV1 system) is exempt, then similar research with *K. lactis* should also be exempt because it is a safer organism by comparison—*K. lactis* does not survive at 37 °C whereas several strains of *Saccharomyces* can survive in temperatures as high as 40 °C. In Europe, *K. lactis* is exchanged freely among investigators, who dehydrate it and mail it; dehydrated cells can be re-cultivated from spores.

Drs. Helen Guthrie and Chris Taron, both from New England BioLabs, explained why this request is coming to the RAC at this time. Use of *K. lactis* in the food industry occurred mostly in Europe, where it was first developed as a host system in the Netherlands in the 1980s. It was one of the first yeasts to be transfected with foreign DNA. The first food-based recombinant product was produced in 1988. The patents for that initial food product were lucrative and the Dutch company held on to the technology. The owner of the patents is now making the technology available beyond Europe to the United States. New England BioLabs decided to petition the NIH to have *K. lactis* and its plasmids added to the list of certified host vector systems.

C. Public Comment

No comments from the public were offered.

D. Committee Motion 4

It was moved by Dr. Yankaskas and seconded by Dr. Fong that the RAC accept the recommended language as proposed by Dr. Kanabrocki. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VI. Day 1 Adjournment

Dr. Zaia, RAC Chair, adjourned Day 1 of the December 2010 RAC meeting at 5:15 p.m. on December 7, 2010.

VII. Day 2 Call to Order and Opening Remarks

Dr. Zaia, RAC Chair, called Day 2 of the December 2010 RAC meeting to order at 8:00 a.m. on December 8, 2010. He welcomed Dr. Chiocca, a new RAC member who attended Day 1 of this RAC meeting via teleconference but was present in person on Day 2.

VIII. Minutes of the September 15-17, 2010, RAC Meeting

RAC Reviewers: Dr. Kohn and Ms. Mallino

Ms. Mallino stated that the comments of Dr. Kohn and herself were incorporated into the minutes document, which was complete and accurate.

A. Committee Motion 5

Ms. Mallino moved and Dr. Kohn seconded that the minutes of the September 15-17, 2010, RAC meeting be accepted. The vote on the motion was 11 in favor, 0 opposed, 0 abstentions, and 0 recusals.

IX. Discussion of Human Gene Transfer Protocol #1010-1068 Entitled: An Open Label Dose-Escalation Study of a Self Complementary Adeno-Associated Viral Vector (scAAV2/8-LP1-hPPCA) for Gene Transfer in Subjects with Galactosialidosis

Principal Investigator:	Arthur W. Nienhuis, M.D., St. Jude Children's Research Hospital
Additional Presenters:	Alessandra d'Azzo, Ph.D., St. Jude Children's Research Hospital (*via teleconference*); John Gray, Ph.D., St. Jude Children's Research Hospital
RAC Reviewers:	Drs. Bartlett, Kahn, and Yankaskas

Drs. Fost, Kohn, and Ross recused themselves from consideration of this protocol due to conflicts of interest.

A. Protocol Summary

The goal of the protocol is the development of gene transfer for galactosialidosis, a lysosomal storage disease associated with a combined deficiency of β -galactosidase and neuraminidase, secondary to a defect of another lysosomal protein, the Protective Protein/Cathepsin A (PPCA). Three phenotypic subtypes are recognized; the early infantile form, the late infantile form and the juvenile/adult group. Hepatosplenomegaly, growth retardation, cardiac involvement and rare occurrence of important neurological signs characterize the late infantile form which is the target group for this gene transfer protocol. A novel, self-complementary AAV vector has been developed which provides liver-specific expression of the transgene, PPCA. The secreted protein is taken up by all somatic tissues where its enzymatic and protective protein activities result in clearance of sialyloligosaccharides and glycoproteins. In preclinical studies, correction of a mouse model which is a phenotypic copy of the human disease has been demonstrated and dose response studies have suggested a potentially effective dose for treatment of human patients. Eligible participants are those with a clinical phenotype of late infantile galactosialidosis and a documented mutation in the PPCA gene localized on chromosome 20q13.1. Participants will be given a vector infusion via peripheral vein and monitored clinically for correction of the phenotype.

B. Written Reviews by RAC Members

Five RAC members voted for in-depth review and public discussion of the protocol. Key issues included the use of a novel transgene to target a new pediatric disease, the limited experience with intravascular delivery of AAV vectors, and the proposed initial dose that is 20-fold greater than that administered to two research participants in a hemophilia trial using the same vector backbone and route of administration. In addition, the ability of the preclinical models to predict systemic biodistribution, gene transduction, toxicity, or immune responses warranted discussion.

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

Dr. Bartlett asked whether PPCA has been shown to be expressed efficiently and secreted from different cell and tissue types, and he wondered why liver-specific expression is proposed for this trial. Noting that the investigators reported that three tumors were detected in the oldest cohort of 19 mice, he queried as

to whether analysis was conducted to determine whether these tumors contained AAV vector DNA. Because the proposed dose is significantly higher than that previously administered intravenously, Dr. Bartlett requested that the investigators comment on the rationale for the infusion rate, the consideration of multiple periodic infusions, and the consideration of monitoring pro-inflammatory cytokines at early timepoints in order to determine whether inflammatory responses to the vector are occurring. Dr. Bartlett asked the investigators to explain how they would deal with early toxicity characteristic of a systemic inflammatory response, if it occurs. He also asked whether preclinical studies had been conducted to investigate interactions of AAV with human blood that might not have been predicted by studies in mouse or nonhuman primates.

Dr. Kahn requested clarification of some issues related to the participant population, including recruitment. He asked about the likely age range of the participants who will have a diagnosis of the late infantile form of galactosialidosis, how many adults are expected to be recruited before the first children, and at what point and dose the first children will be recruited. If children are to be recruited, he noted that the requirements of 45CFR46, Subpart D, must be met in every dose cohort in which children would participate. As a result of this requirement, Dr. Kahn asked the investigators to explain whether and how this trial would offer the potential for direct medical benefits to the individual participants and whether the risk/benefit relationship would be at least as favorable as that presented by available alternative approaches. He suggested that the informed consent document should be written from the perspective of parents or guardians granting permission for participation, since many of the participants are likely to be children. Dr. Kahn stated that the ICD is generally well written, in clear and appropriate language and with sufficient detail and explanation, and offered a few specific suggestions for clarifications, including that the stated requirement for 15 years of follow-up might lead to excessive optimism among participants about the potential benefit of this early-phase trial and that the discussion of reproductive risks and use of birth control might not be appropriate for participants who are young children.

Dr. Yankaskas asked the investigators to describe their evaluation plans if vector or gene expression in tissue other than liver is detected or produces toxicity; he based his concern about toxicity on the significant expression of human PPCA in the gonads of dosed mice. Noting that potential participants would be screened for AAV2 and AAV8 antibodies before dosing, he requested discussion about the cross reactivity of the neutralizing antibody assays for these and other AAV serotypes. Dr. Yankaskas inquired as to the criteria for selecting which immunosuppressive regimen would be used to treat dosing-related hepatitis and asked whether the investigators plan to evaluate AAV and human PPCA presence in the semen of male research participants after they reach puberty. Noting that gonadal transfection might produce long-term effects, he asked whether the potential risks to participants and subsequent offspring were known or could be estimated and, if so, suggested that the investigators amend the informed consent document to reflect those risks.

C. RAC Discussion

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

- Noting that the toxicity and biodistribution studies for this trial are predicated on the Factor IX studies in rhesus macaques, Dr. Bartlett expressed concern about the possibility that the rhesus macaque is not predictive of what could occur in humans. He suggested a more cautious and slower approach might be warranted.

- Dr. Kahn asked the investigators whether they might consider restructuring this proposed trial as a Phase I/II trial with adults, from which they would collect data and be further informed and then conduct a second trial that would include children.

- Dr. Zaia noted that the exclusion criteria are fairly general, including only two items: organ dysfunction that is likely to lead to death in three months and intercurrent infection. He asked if individuals with Hepatitis B or Hepatitis C might also be excluded from participation in this trial.

D. Investigator Response

1. Written Responses to RAC Reviews

PPCA has been shown to be expressed efficiently and excreted from many different cell types. In macaques, the investigators stated that they have found that liver-specific expression can be sustained long-term using the promoter-enhancer combination that is included in the vector proposed for this clinical trial. The liver-specific enhancer-promoter avoids expression in immunostimulatory cells, thereby reducing the risk of an immune response to the transgene product. Despite extensive experience with high-level PPCA expression in the murine model, the investigators have noted no evidence that high-level expression leads to loss of specific activity or antigenic differences in the PPCA protein.

Sixty-two mice were followed by the investigators for periods ranging from 1.75 to 2.25 years after gene transfer, prior to being sacrificed for analysis. Six tumors were found upon sacrifice, but only in the oldest cohort; two were pin-head in size, three were between 3 mm and 5 mm, and an extra-hepatic lesion was 6 mm in maximal diameter. The histopathology of these lesions was mixed, and the DNA copy number in all tumors was significantly less than one copy per cell, suggesting that clonal expansion was not secondary to insertional mutagenesis. These tumors were judged to be representative of what has been described before in aging colonies of mice.

The rationale for the infusion rate is based on the investigators' experience in nonhuman primates as well as the initial experience in their ongoing trial for Hemophilia B. In the nonhuman primate studies, the animals are monitored carefully and no changes in behavior or vital signs have been noted. Interleukin (IL)-6 levels are monitored without any documented increases. The investigators will work with a commercial laboratory that routinely measures IL-1, IL-6, IL-8, and tumor necrosis factor alpha.

In developing the final protocol, the investigators agreed to consider options for monitoring proinflammatory cytokines. If early toxicity is encountered, supportive care will be given as clinically indicated, including the use of intravenous corticosteroids.

The investigators noted Dr. Bartlett's work related to the interactions of AAV with components of complement, which could decrease the efficacy of the vector. However, they were unaware of specific preclinical studies that have investigated interactions of AAV with human red blood cells.

The natural history of the late infantile form of galactosialidosis is not well described. Isolated case reports document the clinical abnormalities noted in the protocol without describing the age of onset, rate of progression, and frequency of occurrence of mutations leading to the late infantile form. Accordingly, in preparation for this gene transfer trial, the investigators plan to perform a survey of available participants by contacting various disease foundations identified in the protocol and all pediatric clinical geneticists throughout the United States and Europe to identify and obtain clinical information on potential participants. The plan is to identify older eligible participants, preferably at least 18 years old, for the first cohort of three to six participants. Only after obtaining data in at least three of the older participants will the investigators consider enrolling younger individuals.

The investigators' prediction of potential efficacy is based on two sets of data and additional results that are being obtained in an ongoing clinical trial for Hemophilia B. In mouse model experiments, the investigators observed elimination of storage material in tissues at a dose as low as $1x10^9$ vg/mouse, with some residual urinary oligosaccharidosis at this dose. During a pre-IND meeting with the FDA, the investigators agreed that additional dose-finding studies should be conducted in the murine model beginning well below the dose of $1x10^9$ vg/mouse, which dose was already tested in an effort to define the minimal effective dose. The investigators' ongoing trial for Factor IX (FIX) deficiency is yielding relevant information in that the dose response in the initial participants seems similar to that observed in rhesus macaques.

With respect to the risk/benefit relationship compared to that presented by available alternative approaches, there are no curative treatments for galactosialidosis that have been tested. Patients are

generally treated with supportive care and treatment of specific organ failure using standard medical intervention including dialysis. In principle, allogeneic stem cell transplantation might be curative but no reports of its use for treating galactosialidosis have appeared. The risk/benefit relationship for allogeneic stem cell transplantation may be acceptable in instances where there is a matched sibling donor, but transplants from alternative donors carry a significantly greater risk. The risk/benefit relationship of the gene transfer approach is contingent on administering a minimal effective dose in the absence of vector-related toxicity, which has not been observed in animal models or in the ongoing Hemophilia B trial.

The informed consent document was developed in accordance with the policies and procedures of the IRB at St. Jude Children's Research Hospital. On page 1 of 16 of the consent document, this wording appears immediately following the title of the protocol: "Note: When we say 'you' throughout this document, we mean 'you or your child.'" This convention was adopted when the IRB decided to eliminate the requirement for separate consent forms for children and adults.

Because the requirement for 15 years of follow-up could lead to therapeutic misconception, the investigators agreed to revise the protocol and the ICD to indicate that long-term annual follow-up is requested, without specifying the duration.

The most definitive biodistribution data available are from a toxicity study performed in rhesus macaques. Three animals received a total of $2x10^{12}$ vg/kg intravenously. Two animals were sacrificed after 60 days along with a noninjected control, and one injected animal and one noninjected control continue to be monitored. No general toxicity (weight loss, temperature elevation, behavior change) was noted at any point during the study. Each of the three macaques that received vector had levels of human FIX expression in the normal range. Laboratory values were generally normal with occasional abnormal values either before or temporally unrelated to the vector administration. The vector genome could be detected in secretion/excretions in each of the three animals that received AAV but cleared in each of these animals at all sites within 10 days. Quantitative PCR analysis of tissues from the two animals that were sacrificed indicated that greater than 98 percent of the vector genome was in the liver, with only trace amounts of vector DNA detectable in other tissues including the gonads. The investigators' ongoing clinical trial for FIX deficiency is yielding transient detection of the genome in body secretions (blood, saliva, urine, stool, and semen samples) after vector administration; the vector genome became undetectable within two to three weeks in each case.

Prior studies in rhesus macaques have confirmed that expression of the liver-specific human FIX expression cassette is limited to the liver. Prior to opening the trial for galactosialidosis, the investigators plan to complete an additional toxicity study in the mouse PPCA-/- model using a dose that is 200-fold higher than the highest dose being considered for use in this proposed clinical trial.

Research participants who develop evidence of immune hepatitis during this study will be given corticosteroids. The details of the dose to be administered are specified in Appendix IV of the protocol along with descriptions of various immunosuppression regimens that have been utilized in efforts to prevent immune hepatitis.

To evaluate AAV and human PPCA presence in the semen of male participants after they reach puberty, the investigators agreed to modify the protocol to include this statement: "To evaluate the potential for vertical transmission of scAAV2/8, semen samples will be obtained at baseline and during weeks 1, 3, 6, 9, and 12 until three sequential samples are negative for vector genomes using our PCR assay. Participants will be counseled to consider sperm banking prior to vector administration and to practice barrier contraception until three serial weekly semen samples have been declared as negative."

The risk of germline transmission has been studied extensively in a rabbit model with AAV2 and with AAV8 vectors. Vector was detected in semen in this animal model following injection but disappeared in a dose-dependent and time-dependent manner. The rate of clearance was serotype independent. AAV2 or AAV8 sequences were detected in the semen of vasectomized animals that lack germ cells, suggesting that structures of the genitourinary tract, as well as potentially the testes, contribute significantly to vector shedding in the semen. No vector was found in semen after a third spermatogenic

cycle with either serotype vector. Animals that received an AAV8 vector were followed during 15 months post-injection; no recurrent vector DNA sequences were observed in any of the semen samples tested after obtaining three consecutive negative PCR tests. Extensive biodistribution studies performed in these animals indicated that only the liver contained significant copies of the vector genome.

Because gonadal infection might produce long-term effects, the investigators agreed to amend the informed consent document to add the following language:

> After the vector is infused, it is possible that the vector may go to different tissues through the body, but not only to the liver as intended. There is the theoretical risk that vector particles can enter the genetic information (chromosomes or DNA) of germ cells or semen and potentially damage the DNA. In that case it is possible to pass the vector genes or damaged DNA on to an unborn child and possibly later to this child's children. The risks to an unborn child or to any offspring of this child are unknown. Because of these concerns, we are asking participants who are past puberty to use a reliable barrier method of contraception for three to six months. Although we wish to make you aware of this potential risk, there is no evidence that similar vectors have gone into germ cells in experimental animals or prior participants in a gene transfer trial for a form of hemophilia.

2. Responses to RAC Discussion Questions

Dr. Nienhuis noted that if the investigators identify up to 10 adults, they could propose a Phase I trial at two doses to determine safety, followed by a "Stage 2" trial focused on children. He noted that the principle of starting in adults and then dosing children is well established in oncology trials.

As discussed with the FDA, the investigators do not plan to administer immunosuppression because of experience, in at least one other trial using serotype 1, showing a risk for hepatitis. The process the investigators decided upon was to conduct the initial protocol without routine immunosuppression, and if a research participant develops hepatitis that individual would be given high-dose corticosteroids. Following such an event, the investigators would stop enrolling participants and would amend the protocol to incorporate an immunosuppression regimen.

The investigators stated that the exclusion criteria were written to be general because of the relatively early stage in defining the protocol. The goal is to exclude individuals with intercurrent medical problems that are significant and could compromise the interpretation of this clinical trial.

The investigators explained that the vector dose will be informed by additional mouse studies and the Factor IX clinical trial currently underway. While they will want to use the lowest dose that will impact the disease, their inclination is to be aggressive on the first dose because no good alternate treatment exists.

Dr. Nienhuis stated that the investigators are beginning to design the survey that is intended to uncover the number of adults who might participate in this trial.

E. Public Comment

Ms. Rooney noted that the ICD includes no mention of the actual procedures each participant will undergo when receiving the vector. She suggested adding this information.

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.

<u>Clinical and Trial Design Issues</u>

- The proposed dose is primarily based on the results of the rhesus monkey studies and the ongoing hemophilia B trial, which uses the identical AAV vector expressing a Factor IX transgene.

While likely predictive, it is not certain to what extent the data from those studies will predict the experience with the scAAV2/8LP1hPPCA vector in the galactosialidosis patient population. Taking into account any additional data from the preclinical or hemophilia B studies, consideration should be given to the use of a lower initial dose.

- Given the risks described in the protocol of immune hepatitis associated with the use of this vector that will primarily target the liver, the exclusion criteria should be more specific with respect to enrollment of participants with active liver infections and/or compromised liver function.

Ethical, Social, and Legal Issues

- The investigators propose to enroll older children and preferably adults prior to younger children, an approach that would be appropriate given the novelty of the protocol. However, the protocol does not clearly explain the enrollment plan for recruiting older participants prior to recruiting younger children. The investigators should clarify for each cohort how many older children or adult participants they propose to enroll prior to moving to younger participants.

- The consent document is generally well written in language that is clear and appropriate. It could be improved by including additional information regarding the procedures involved in the administration of the vector, such as proposed length of stay in the hospital, and any additional blood draws or tests.

G. Committee Motion 6

Dr. Zaia orally summarized the RAC recommendations that will be included in the letter to the investigators expressing the comments and concerns of the RAC. It was moved by Dr. Kahn and seconded by Dr. Bartlett that the RAC approve these summarized recommendations. The vote was 14 in favor, 0 opposed, 0 abstentions, and 3 recusals (Drs. Fost, Kohn, and Ross).

[At this point in the RAC meeting, Dr. Fong took over as Acting Chair of the RAC. Dr. Zaia left the meeting room.]

X. Discussion of Human Gene Transfer Protocol #1010-1076 Entitled: Phase I Clinical Trial of Autologous Alpha-Folate Receptor Redirected T Cells Administered Intravenously in Ovarian Cancer Patients

Principal Investigator:	George Coukos, M.D., Ph.D., University of Pennsylvania School of Medicine
Additional Presenters:	Lana E. Kandalaft, PharmD, Ph.D., University of Pennsylvania School of Medicine
Sponsor:	Daniel J. Powell, Jr., Ph.D., University of Pennsylvania School of Medicine
RAC Reviewers:	Drs. Buchmeier, Sarzotti-Kelsoe, and Strome

Drs. Fost, Kohn, Ross, and Zaia recused themselves from consideration of this protocol due to conflicts of interest.

A. Protocol Summary

Ovarian cancer is the fifth most common cancer in women, with about 1 in 55 women developing an ovarian malignancy during her lifetime. Approximately 21,650 new cases occur annually in the United States, with 15,520 deaths estimated in 2008, making ovarian cancer the most common cause of death from gynecologic malignancy.

At the time of diagnosis, the majority of women with ovarian cancer have disease that has already spread throughout the abdomen. For the vast majority of these women, conventional treatment with surgery and chemotherapy fail to provide a long-term cure. For patients with recurrent ovarian and primary peritoneal cancer, response to second-line agents is less than 30 percent. T-cell transfer has historically shown promise for treating cancer, and using modified autologous T cells to target a tumor antigen and stimulate effector T-cell function has shown promising results. The proposed trial will test the safety and feasibility of genetically engineered T cells to treat recurrent ovarian cancer.

Epithelial ovarian cancer comprises a majority of the ovarian malignancies and typically occurs in women between the ages of 40 and 65 years old. Between 60 and 70 percent of patients present with Stage III or Stage IV disease, with an associated 5-year survival rate of less than 25 percent. Improvements have been made in recent years in treating advanced epithelial ovarian cancer, but the most common outcome is initial tumor reduction after primary surgery and adjuvant chemotherapy, followed by relapse and eventual death from progressive disease. New approaches are needed to improve the outcome for these women.

Much hope has accompanied the development of gene transfer concepts for cancers of various sites. However, to date, proof of efficacy of this treatment modality is lacking. The hypothesis driving the proposed clinical study is that autologous T cells can be altered genetically to encourage binding of immune cells to tumor cells, thereby activating those immune cells to kill tumors. To test this hypothesis, the investigators propose a Phase I study in which research participants with advanced ovarian cancer will be injected intravenously with autologous T cells transduced with chimeric anti-alpha-folate receptor (anti-α-FR) immunoreceptors. The use of genetically redirected, autologous lymphocytes transfected with a chimeric immunoreceptor (CIR) specific for an ovarian tumor antigen, alpha-folate receptor is hypothesized to increase avidity to tumors and delay ovarian cancer disease progression by selectively destroying tumor cells. Alpha-folate receptor is a cell-surface molecule over-expressed on a large fraction of carcinomas, and thus is an attractive target for immunotherapy. Lentiviral vectors are used to express a single-chain variable antibody fragment (scFv) that binds alpha-folate receptor and which is fused to the CD3-zeta signaling domains of the T cell receptor (TCR) and additional costimulatory domains CD28, and CD137 (4-1BB) to yield a chimeric immune receptor (CIR) that allows T cells to be redirected against the "tumor surface target alpha-Folate Receptor (α-FR CIR). When stimulated by alpha-folate, lentivirally transduced T cells proliferate and secrete multiple cytokines, features characteristic of central memory T cells. When injected intravenously into lymphopenic mice engrafted with large pre-established tumors, the α-FR-CIR engineered T cells reduced tumor burden, and in some cases resulted in complete eradication of the tumors. Based on this preclinical data, a phase I study is proposed to determine the safety, tolerability and engraftment potential of anti-α-FR CIR modified T cells administered IV in patients with ovarian cancer.

B. Written Reviews by RAC Members

Five RAC members voted for in-depth review and public discussion of the protocol. Key issues included that, while the α-FR is only expressed in low levels in normal issues, the potential for on-target, off-tissue toxicity is of concern; in addition, the potential immunogenicity of the murine sequences from the monoclonal antibody deserves further consideration.

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

Dr. Buchmeier expressed concern that the ICD is written in a way that minimizes the potential risks associated with this experimental therapy, which includes autoimmune attack of the re-targeted T cell to endogenous FR-expressing cells. His primary concern with the protocol was the scarcity of information in human studies about the effect of targeting the engineered T cells against the folate receptor. Although the strategy appears to be well thought out and experimentally sound, Dr. Buchmeier noted that uncertainty persists about the potential effects on normal tissues expressing the folate receptor. He explained that this concern takes two forms: (1) the risk of triggering an autoimmune attack on normal tissues as well as the antitumor activity and (2) concern about the (real or theoretical) risk of triggering an

aberrant pathological cytokine response in the tumor tissue. He requested that the investigators outline the course of action to be taken in the event of a significant on-target, off-tissue response.

Noting that the rationale of the protocol is to eliminate regulatory T cells (Tregs) and other elements of the immune system that may act as cytokine sinks, Dr. Sarzotti-Kelsoe asked how the investigators plan to address the possibility that Tregs may be present within the autologous T-cell populations that will be transduced by the lentivirus vector expressing αFR CIR and then re-injected into the research participants*. Dr. Sarzotti-Kelsoe asked that the investigators clarify whether the levels of the tumor marker CA-125 will be used to assess the results of gene therapy. She* requested confirmation that the route of administration in this protocol would be intravenous and clarification that participants in cohort 1 would receive three injections of the CIR T cells but not the three doses of the chemotherapy drugs cyclophosphamide and fludarabine (cy/flu), as will be administered to cohorts 2, 3, and 4.

Dr. Strome requested that the investigators share data that show percentages of cellular death in a solid tumor model, indicate whether there is a limited effect on normal cells over time, discuss substantive information regarding this construct relating to potential mutagenesis, and provide any new evidence about the potential for uncontrolled proliferation. Regarding dosing, he asked why the proposed dosing sequence was chosen, what data supports the suggestion of detectable levels at six months, and how long therapeutic levels are expected to be maintained. Dr. Strome wondered why the investigators are waiting for clinical development of a humanized monoclonal for later-stage clinical trials, noting that the construct proposed for this protocol is a mouse monoclonal, which could be more immunogenic than a human construct. He noted that the investigators acknowledge that tumor-line uniformity in knockout mice is problematic, and asked why they have not used another animal model for preclinical studies. Within the ICD, Dr. Strome suggested several clarifications and requested that terminology that can be understood by all potential participants be used. He further stated that all costs for AEs not covered by insurance should be covered by the institution. Dr. Strome asked what measures will be in place to ensure that all prospective participants will receive the same information in the informed consent process.

C. RAC Discussion

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

- Dr. Fong asked about the standard of care for surgery.
- Dr. Chiocca requested that the investigators discuss how they plan to monitor for toxicities, especially neurologic toxicities that could be seen as α-folate receptor can be expressed in the choroid plexus.
- Dr. Fong requested clarification as to whether research participants could undergo apheresis a second time if the cells from the first apheresis did not meet the release criteria and could not be used. .

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators agreed to reword the informed consent document to reflect the risk associated with the potential adverse effects of the gene transfer. In particular, they will describe in lay terms recent unexpected toxicity and risk of death from infusion reaction, hypersensitivity reaction, cytokine “storm,” or T-cell autoimmune pathology.

The investigators agreed to modify the language in the ICD to include specific potential risks and monitoring for potential toxicities, including renal, pulmonary, and central nervous system toxicities, which are tissues with normal folate receptor expression.

T cells transduced with anti-α-FR scFv cells have been previously tested in one clinical trial in humans—a 14-participant trial with two arms evaluating a CIR targeting the folate receptor and linked to the Fc receptor zeta signaling chain. Grade 3 and 4 AEs were observed in Arm 1 but were attributed to IL-2

administration; no SAEs were attributed to T-body administration. Although the persistence of modified cells was poor and did not exceed three weeks, these data provide early proof of safety that short-term toxicities in an immunocompetent host are limited with doses up to $5x10^{10}$ T cells. In the proposed trial, the investigators expect T cells to persist longer and to have more powerful activity, because of lymphodepletion and costimulatory signaling. The proposed entry dose is approximately one log lower than in the above trial, and a split-dose approach is proposed as further precaution. The investigators reiterated that participants will be monitored carefully for SAEs.

In multiple clinical studies, the transfer of unselected peripheral blood lymphocytes (including Treg cells), which were genetically redirected for tumor specificity, mediated potent antitumor effects after infusion. This indicates that, while a small subset of Treg cells may exist in genetically engineered T cells, those Treg cells are not sufficient in number or potency to disrupt the potent antitumor effects of adoptive immunotherapy. The study will monitor for Treg reconstitution and may explore the utilization of Treg depleting strategies, such as large-scale *ex vivo* CD25 depletion to improve the net potency of the transferred T cell population in future trials

The investigators agreed to clarify throughout the protocol that the only route of administration will be the intravenous route. They also agreed to clarify that cohort 1 will not receive cy/flu.

The investigators provided several preclinical studies in the Appendix M submission of this protocol to demonstrate the *in vitro* and *in vivo* antitumor cytolytic activity of the α-FR CIR gene transfer system and its payload. In a xenogeneic model of advanced solid ovarian cancer, large established human ovarian cancer is eliminated by intratumoral, subcutaneous, or intravenous infusion of α-FR CIR T cells in immunodeficient mice. These results validate the antitumor potential of human T cells transduced to express α-FR CIR.

Whether α-FR CIR T-cell therapy will have an effect on normal cells over time in humans is not known. Because the proposed construct carries costimulatory domains and T cells are expected to be more powerful than those used in prior studies, the investigators have designed a dose escalation strategy that starts at a lower dose; they propose to use a within-patient, split-dose strategy for the Phase I testing of the costimulated α-FR CIR T cells to address the potential for recognition of normal cells.

To date, there are no reported cases of uncontrolled proliferation as a result of mutagenesis in redirected human T cells transduced with retroviruses or lentiviruses. To assess potential for uncontrolled proliferation, the investigators evaluated the growth kinetics of transduced T cells from several donors and tested for proliferation differences between the untransduced cells and the various α-FR CIR constructs. No enhancement of proliferation was observed in any of the α-FR CIR cultures.

To evaluate the safety of vector-modified cells in the presence of antigen, NOD/SCID/IL2r-gamma(null) mice were engrafted with human acute B-cell lymphocytic leukemia, followed two weeks later by escalating doses of chimeric antigen receptor expressing T cells containing a mixture of chimeric receptors. The long-term follow-up animals were followed until CIR T cells were no longer detected or until old age, and then were sacrificed for analysis. In this animal model, no evidence of toxicity or uncontrolled proliferation of vector-transduced cells was detected.

In this protocol, the investigators propose to administer T cells with a split dose approach, whereby each participant will receive 10 percent of the prescribed dose on Day 1, 30 percent on Day 2, and the remaining dose (60 percent) on Day 3. (This dose sequence was chosen as a result of discussion held during the RAC Safety Symposium on June 15, 2010.) The investigators explained that they decided to administer the entire dose within three days in order to take advantage of the lymphopenia window following cy/flu administration. A delay of 24 hours between the three doses is expected to be sufficient time for acute AEs to manifest.

In a human immunodeficiency virus study, gene-marked cells persisted in the blood for more than 10 years after transfer, however, it is not known how long therapeutic levels of T cells need to be maintained – or at what levels – for cancer therapy. Based on previous experience, the window of therapeutic

effectiveness is often within the first month after T-cell infusion, and generally research participants who experience objective and durable responses have detectable T cells persisting in circulation. This proposed study will monitor T cells in blood to evaluate their persistence and correlation with objective response or clinical benefit.

The investigators explained that prior studies using gene-modified T cells expressing xenogeneic transgene have demonstrated that humoral immune response can be elicited when the modified T cells are administered to immunocompetent research participants. However, in the setting of host preconditioning with lymphodepletion, transfer of autologous T cells redirected to tumor-associated antigens using mouse scFvs or TCRs can mediate tumor regression and provide meaningful clinical benefit in patients with advanced hematological and solid cancers. Transgene immunogenicity is not known to significantly impair the function or persistence of adoptively transferred T cells in this lymphopenic environment, in which humoral responses are severely compromised.

Tumor cell line uniformity is not a problem in the mouse model. SKOV3 is a well-established human ovarian cancer cell line that was selected from a panel of cell lines for use in the development of the investigators' xenogeneic model of human ovarian cancer. This model is the best available to date.

The investigators agreed to incorporate an explanation, in lay terms, of the rationale for using cy/flu by stating that adoptive T-cell therapy has worked better in previous clinical trials when administered following a short course of high-dose chemotherapy with cy/flu.

Informed consent will be obtained by the principal investigator, or by the sub-investigators, or the research nurse who will be trained by the principal investigator prior to the initiation of the trial. The investigators will employ a checklist of the important information that should be relayed to prospective participants, to ensure that all individuals receive the same information.

2. Responses to RAC Discussion Questions

Dr. Coukos explained that the investigators intend to record participants' CA-125 levels but are not planning to use that measure to make decisions regarding response or evaluations. Retrospectively, once this and additional trials are completed, it will be possible to consider how CA-125 levels reflect on objective tumor responses in the context of cellular immunotherapy. Currently, that information is not known.

With regard to the standard-of-care treatment, Dr. Coukos explained that surgery, followed by chemotherapy, is always indicated. Surgery also is indicated in patients with recurrent disease who fulfill several criteria, primarily that their tumors are resectable. Based on computed tomography imaging, tumor masses can be removed if the result will not be excessively harmful to the patient. A case in which surgical debulking will dramatically reduce tumor volume is also an indication for surgery. A patient who presents with a resectable tumor and sensitivity to platinum may be considered by some clinicians to warrant surgery. All of these individuals will not be included in this study. For this trial, Dr. Coukos reiterated that the investigators will include patients who have exhausted first-line and second-line agents and are platinum resistant; they must have completed at least two prior regimens of chemotherapy.

Dr. Coukos explained that neurologic toxicities would be monitored by teaching the research participant and family to recognize early changes in mental status, cognitive changes, and behavioral changes, as well as the classic signs of encephalitis, meningitis, and increased intracranial blood pressure. All of this information will be included in the clinical protocol. The investigators are working with neurologists at the University of Pennsylvania, one of whom has expertise in autoimmune disease of the brain, to define and capture all the possible manifestations of an early autoimmune breakthrough in the brain as well as what needs to be done when that individual shows up at the emergency room. The neurology team will develop a specific protocol focused on how to evaluate and treat neurologic toxicities, should they occur.

In response to a question about whether research participants could be undergo a secondapheresis, Dr. Coukos clarified that re-apheresis could not be done immediately as the subject will have received

lymphodepleting chemotherapy. However, once a research participant recovers and if additional aliquots of the original apheresis still exist, re-transduction could be accomplished. This possible process is described in the protocol.

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 and Trial Design Issues

- For safety reasons, the protocol will infuse the cells over three days in escalating amounts (10 percent on Day 1, 30 percent on Day 2, and 60 percent on Day 3). Splitting of doses is a relatively new strategy that is designed to identify acute toxicities prior to administration of a full dose, at which point it may be more difficult to reverse the acute toxicity. However, the optimum interval between infusions is not known. If there is no compelling reason to infuse the final dose on Day 3, in the interest of safety it may be prudent to infuse the final dose on Day 5, at least in the initial cohorts. This will allow additional time to evaluate for any toxicity from the first infusions that may be predictive of an adverse reaction to the final infusion.

- The protocol states that lymphodepleting chemotherapy "eliminates regulatory T cells." However, as the investigators acknowledge in their response to the written RAC reviews, the transduced cells will also include T regulatory cells. This should be clarified in the protocol.

- The original protocol submitted to the OBA did not contain detailed information regarding proposed management of potential AEs that might occur due to infusion of the transduced T cells, including AEs arising from potential off-target T-cell activity (i.e., on normal tissue that expresses the alpha folate receptor). The information regarding management of AEs that was submitted in the written responses should be incorporated into the protocol.

Ethical, Social, and Legal Issues

- The construct in this protocol uses a murine-derived antibody but the investigators note that they anticipate using a humanized version in future trials to minimize the risk of an immune reaction against the modified T cells. The ICD should explain the rationale for proceeding in the initial trial with the murine-derived construct rather than waiting for development of a humanized construct.

- There is the possibility that a participant could undergo apheresis and receive the lymphodepleting chemotherapy but their gene-modified T cells could fail to meet release criteria. In that situation, there may be two options: 1) transduce stored cells from the first apheresis or 2) repeat the apheresis after recovery of lymphocyte and other blood counts. While this is likely to be a rare event, it would be helpful to discuss in the ICD this scenario and the proposed plan to address it.

G. Committee Motion 7

Dr. Fong summarized the RAC recommendations to be included in the letter to the investigators expressing the comments and concerns of the RAC. It was moved by Dr. Yankaskas and seconded by Dr. Buchmeier that the RAC approve these summarized recommendations. The vote was 13 in favor, 0 opposed, 0 abstentions, and 4 recusals (Drs. Fost, Kohn, Ross, and Zaia).

XI. Closing Remarks and Adjournment

Dr. Fong thanked the RAC members and the OBA staff, and adjourned Day 2 of the December 2010 RAC meeting at 11:30 a.m. on December 8, 2010.

[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.

This Minutes document will be considered formally 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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Recombinant DNA Advisory Committee

Attachment I: RAC Roster
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Attachment II
Public Attendees

Terry Anderson, spouse of myositis patient
Abe Bassan, bluebird bio, Inc.
Wilson Bryan, FDA
Christine Duncan, Children's Hospital Boston
Mitchell Finer, bluebird bio, Inc.
Denise Gavin, FDA
Ying Huang, FDA
Kathleen Kirby, bluebird bio, Inc.
Xiaobin V. Lu, FDA
Rachel Salzman, The Stop ALD Foundation
Ramjay Vatsan, FDA
Gabor Veres, bluebird bio, Inc.
Fraser Wright, University of Pennsylvania

Attachment III
Abbreviations and Acronyms

6MWT	6-minute walk test
AAV	adeno-associated virus
AE	adverse event
ALDP	adrenoleukodystrophy protein
anti-α-FR	anti-alpha-folate receptor
BL	biosafety level
BMD	Becker muscular dystrophy
CARs	chimeric antigen receptors
CCALD	childhood cerebral adrenoleukodystrophy
CIR	chimeric immune receptor
cy/flu	cyclophosphamide and fludarabine
DHHS	U.S. Department of Health and Human Services
DLT	dose-limiting toxicity
FDA	Food and Drug Administration, DHHS
FIX	Factor IX
GTSAB	Gene Transfer Safety Assessment Board
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSCs	hematopoietic stem cells
HSCT	hematopoietic stem cell transplantation
HV1	host vector 1
ICD	informed consent document
IND	investigational new drug
IBC	institutional biosafety committee
IL	interleukin
IRB	institutional review board
K. lactis	*Kluyveromyces lactis*
MRI	magnetic resonance imaging
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PBMCs	peripheral blood mononuclear cells
PBSCs	peripheral blood stem cells
PPCA	Protective Protein/Cathepsin A
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
scFV	single-chain variable fragment
sIBM	sporadic inclusion body myositis
TCRs	T-cell receptors
Tregs	regulatory T cells
vg	vector genomes